CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214916Orig1s000

OTHER REVIEW(S)

Clinical Inspection Summary

Date	8/13/2021
From	Phuc (Phil) Nguyen M.D., Medical Officer Karen Bleich M.D., Team Leader Kassa Ayalew M.D., M.P.H., Branch Chief/ Interim Division Director Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Gary Chiang M.D. , Medical Officer Amy Woitach D.O., Team Lead Kendall Marcus M.D., Division Director Division of Dermatology and Dentistry
NDA	214916
Applicant	Cara Theraputics Inc.
Drug	Difelikefalin
NME	Yes
Therapeutic Classification	Antipuritics
Proposed Indication	Treatment of moderate-to-severe pruritus associated with chronic kidney disease (CKD-aP) in adult patients undergoing hemodialysis (HD)
Consultation Request Date	2/8/2021
Summary Goal Date	8/13/2021
Action Goal Date	8/13/2021
PDUFA Date	8/23/2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two phase-3 studies, **CR845CLIN3102** and **CR845CLIN3103,** were submitted to the Agency in support of a New Drug Application (NDA 214916) for IV difelikefalin for the above proposed indication. Three clinical investigators (Drs. Kumar, Aeysu, and Awad) and the Sponsor (Cara Theraputics Inc.) were selected for surveillance clinical inspections.

The inspection of Dr. Kumar revealed a number of findings regarding the conduct of both studies that may impact the reliability of the study data generated at the site. The findings are summarized below and discussed further in Section III Results.

- Subject [redacted] (b) (6) (Study CLIN3103, Difelikefalin arm) received 16 doses of diphenhydramine during hemodialysis (HD) sessions during the study according to source HD worksheets and yet was reported in the submission as not having received any

concomitant anti-itch medications. The inspection found that hemodialysis worksheets, despite being listed as a source record to be printed and maintained within subject binders, were not reliably included in subject binders and additional instances of unreported concomitant medications were identified upon review of the HD records. Additionally, Dr. Kumar and his staff were unaware of the existence of additional HD records (including nursing notes) that were captured during HD sessions for the study subjects.

- Deficiencies in the capture of endpoint data were identified for Subject (b) (6) (Study CLIN3102, Difelikefalin arm). In this case, the subject's intended worst-itch NRS response was ambiguous on three occasions, site staff had initialed the endpoint worst-itch NRS worksheet selection despite training instructions that no one other than the subject should write in that space, and in all three cases, the lower of the ambiguous worst-itch NRS results was chosen and entered into the EDC with no effort by Dr. Kumar to resolve the ambiguity.
- There were errors in investigational product (IP) dosing and administration. Subjects (b) (6) (Study CLIN3103, difelikefalin (b) (6) (Study CLIN3103, difelikefalin arm), and (b) (6) (Study CLIN3103, placebo arm), repeatedly received the wrong dose and there were several instances in which the source records indicate that the protocol-required IV saline flush was not administered when required. The dosing errors were found to be caused by incorrect instructions contained within source template documents created by Dr. Kumar and his staff.

Following the inspection of Dr. Kumar, internal discrepancies in the concomitant medication data were identified during the review of subject line listing for Subject (b) (6) (Study CLIN3102, placebo arm) and Subject (b) (6) (Study CLIN3102, difelikefalin arm), who had been enrolled by Dr. Kumar. The subjects were stratified as not having been on any anti-itch medication, yet the prior and concomitant medication data indicated that both subjects were on diphenhydramine prior to enrollment.

The inspections of Drs. Aeysu and Awad revealed no significant findings. The scope of the inspections did not include a review of the HD records for concomitant medications. The inspection of the study sponsor, Cara Therapeutics found no significant concerns with study conduct or oversight.

Based on the inspection findings, OSI recommends conducting a sensitivity analysis to assess the validity and robustness of the primary analysis results by excluding the data generated by Dr. Kumar. Additionally, we note that the study protocols do not specifically state that HD records should be reviewed to assess anti-itch medication use during HD before and during the study. It is not known if other clinical investigator sites adequately reviewed HD records to capture the use of concomitant anti-itch medications during HD. OSI recommends an additional sensitivity analysis to assess the results from the primary analysis by excluding subject reported as not having used any concomitant anti-itch medications during the study.

II. BACKGROUND

Cara Therapeutics Inc. seeks approval of difelikefalin as an IV treatment for moderate-to-severe pruritus associated with chronic kidney disease in patients undergoing hemodialysis. Difelikefalin is a K-Opioid Receptor (KOR) agonist, with reportedly negligible activity at other opioid receptors and limited access to the central nervous system (CNS). Per the sponsor, Chronic kidney disease-associated pruritus (CKD-aP; also known as uremic pruritus) is a chronic condition in patients with chronic kidney disease, particularly those undergoing hemodialysis. Difelikefalin is intended to work primarily in the peripheral nervous system to reduce this pruritus.

Data from two phase-3 clinical studies were submitted for this NDA.

Study CR845CLIN3102 (Study CLIN3102)

- Title of Study: A Study to Evaluate the Safety and Efficacy of CR845 in Hemodialysis Patients With Moderate-to-Severe Pruritus

Per the sponsor, this study was intended to be a domestic, multicenter, placebo-controlled, randomized, 12-week, double-blind study with up to 52-week open-label extensions to evaluate the safety and efficacy of difelikefalin at a dose of 0.5 mcg/kg administered after each hemodialysis (HD) session 3 times a week, in HD subjects with moderate-to-severe pruritus.

Eligible subjects were to be males or non-pregnant females aged 18 years or older undergoing hemodialysis 3 times a week for end-stage renal disease (ESRD), and a mean baseline Worst Itch-Numerical Rating Scale (WI-NRS) score >4. Subjects were to be stratified-randomized in a 1:1 ratio to receive either CR845 0.5 mcg/kg IV or matching placebo IV during the Double-blind Treatment Period. Stratification was dependent on the use of concomitant anti-itch medication, and presence or absence of specific medical conditions, notably a history of falls, mental status changes, confusional state, gait disturbance, or movement disorders.

The protocol specified the following regarding medications, adverse events, and anti-itch medication use. Concomitant medications are to be continuously recorded starting at the Screening Visit until the end of the Discontinuation Period or Early Termination Visit. The use of antipruritic meds during the study will be recorded on an ongoing basis starting at screening. A criterion for exclusion from the study is new or change of treatment received for itch including antihistamines and corticosteroids within 14 days prior to screening. Lastly, no new medication to treat itch should be initiated as these medications are restricted.

Though not specifically highlighted in study protocol language, medical records including Hemodialysis treatment records for at least a 3-months period were to be reviewed prior to screening, as patients will have to be stratified-randomized according to their use or non-use of concomitant medications to treat itch during the pre-randomization week.

During the Double-blind Treatment Period, subjects would continue to report their WI-NRS score on a daily basis, covering the previous 24 hours. During selected study visits, they were to complete other patient-reported outcome (PRO) measures (Skindex-10 Scale, 5-D Itch Scale, and

Patient Global Impression of Change [PGIC]). Subjects were to be trained in the use of the WI-NRS scores and related Patient Reported Outcome (PRO) measures. Subjects were to be instructed to record PRO measurements, including WI-NRS scores, at a similar time of day, whether in the dialysis unit (on dialysis days) or at home (on non-dialysis days).

The primary endpoint was based on achieving ≥ 4 (and ≥ 3)- point improvement from baseline with respect to weekly mean of the daily 24-hour worse-itch numeric rating scale (WI-NRS).

Patients who received at least 30 doses of study drug (either active or placebo) during the 12-week Double-blind Treatment Period and continue to meet other eligibility criteria were to have the option to receive open-label CR845 for an additional 52 weeks.

Per the study report, this study was conducted at 56 sites in the United States, with 3 centers only screening subjects. The first subject was enrolled February 6th, 2018, and the last subject completed on April 14, 2109 for the double-blind phase. A total of 503 subjects were screened and 378 subjects were randomized and allocated to equal placebo and difelikefalin arms during the Double-Blind treatment period.

Study CR845CLIN3103 (Study CLIN3103):

- Title of Study: A Global Study to Evaluate the Safety and Efficacy of CR845 in Hemodialysis Patients With Moderate-to-Severe Pruritus

Per the sponsor, this study was intended to be an international, multicenter, placebo-controlled, randomized, 12-week, double-blind study with up to 52-week open-label extensions to evaluate the safety and efficacy of difelikefalin at a dose of 0.5 mcg/kg administered after each hemodialysis (HD) session 3 times a week, in HD subjects with moderate-to-severe pruritus. The protocol is otherwise similar to CLIN3103, with a protocol difference being a lack of a discontinuation period before the open label extension phase.

Per the study report, this study was conducted at 75 sites across 10 countries, with the majority being US sites. The first subject was enrolled July 20th, 2018, and the last subject completed on 28th February 2020. A total of 620 subjects were screened, and 473 subjects were randomized and allocated to equal placebo and difelikefalin arms during the Double-Blind treatment period.

III. RESULTS (by Site)

1. Kumar, Jayant
   3821 Masthead Ne, Albuquerque, NM 87109
   Study: CR845CLIN3102
   Site Number: 116
   Study: CR845CLIN3103
   Site Number: 840023
   Dates of Inspection: 3/4/2021-3/5/2021; 3/8/2021-3/25/2021; 5/3/2021-5/7/2021; 5/10/2021

This inspection was conducted on-site. For study CLIN3102, the site enrolled 22 subjects. For study CLIN3103, the site enrolled 13 subjects. Records reviewed included training and delegation records; authority and administration records; financial disclosures; institutional review board documents, and sponsor monitor reports. For 8 subjects for study CLIN3102, and 9 subjects for study CLIN3103, record review included: source records consisting of ICFs, medical histories, concomitant medications, adverse events, study drug administration, lab results, progress notes, hemodialysis (HD) records, NRS worksheets, blinding and inclusion/exclusion criteria; primary endpoint efficacy data; protocol deviations; and data line listings.

Subject (b) (6) (Study CLIN3103, difelikefalin arm) was randomized on (b) (6) to treatment with difelikefalin and stratified to "no anti-itch medications". The subject level data listing for this subject contained no entry for diphenhydramine as a prior or concomitant medication at any time during the study. However, source HD worksheets reviewed at the site record 16 doses of diphenhydramine administered from (b) (6) concurrent with the start of IP administration (7 during DB period).

Examination of Subject (b) (6) (Study CLIN3103, difelikefalin arm) day one HD treatment sheet showed notation that classified diphenhydramine as both a 'new medication' and 'Prior Concomitant Medication (PCM)' on Day 1 of study treatment. It is unknown if the subject received Diphenhydramine in the run-in period. Thus, either the subject was stratified incorrectly, or the subject was started on anti-itch medications on day 1 of the study; neither of which was reported.

Additional discrepancies regarding the use of anti-itch concomitant medications were identified by the site monitor in the monitoring records reviewed at the site. Following the inspection of Dr. Kumar, a review of subject line listing for stratification and for prior and concomitant medication found the two subjects below as having unreported use of anti-itch medication reveal, and these internal discrepancies and are present in the submitted data in Table 1.

Table 1: Discrepancies within submitted subject level data listings for Study CLIN3102

Subject #	**Treatment Arm, Randomization Date**	**Anti-itch Actual strata (Data Listing)**	**Prior and Concomitant med (Data Listing)**
(b) (6)	Placebo, (b) (6)	No	Diphenhydramine prn since (b) (6)
	Difelikefalin, (b) (6)	No	Diphenhydramine prn for pruritis since (b) (6)

Additional unreported concomitant medications identified in source HD flowsheets include:

- Subject (b) (6) (Study CLIN3102, randomized to difelikefalin arm on (b) (6)) received Clonidine HCL (0.100 mg) on (b) (6) and Tuberol (0.100 ml) on (b) (6)
- Subject (b) (6) (Study CLIN3103, randomized to difelikefalin arm on (b) (6) received Clonidine HCL (0.100 mg, oral) on (b) (6), after oral use of the drug was to have stopped on (b) (6) because of the start of the use of clonidine patch on (b) (6).

According to the Investigator Source Agreement for Study CLIN3103 (signed by the CI on 2/2019), hemodialysis flowcharts were considered to be a source records and were to be stored in paper form in subject charts. This also applied for Study CLIN3102. According to the study training documents from the study sponsor, HD flowsheets were to be reviewed for the time period of three months prior to the first dose of treatment. In the following instances, the HD flowcharts were not maintained in the subject charts at the site:

- Subject (b) (6) (Study CLIN3102, placebo arm): There were no HD worksheets in subject records for the 3 months prior to first dose of study drug. The site staff were able to provide these upon request during the inspection by requesting the records from the dialysis center. There was no evidence that the records had been reviewed prior to the inspection.
- Subject (b) (6) (Study CLIN3102, placebo arm): There were no HD flowsheets for (b) (6) in the subject's binder, days for which study drug was administered with dialysis treatments.

Study staff did not have direct access to the electronic medical record system at the dialysis centers in which subjects' dialysis records were created and maintained. In addition to HD flowcharts, additional subject medical records were created during HD sessions at the dialysis centers including Clinical Notes and Dialysis Rounds. Dr. Kumar and study staff were not aware of the existence of these additional provider records.

Patient's Primary Care Provider (PCP) medical records were not consistently obtained in a timely manner, despite an SOP document at the site instructing staff to obtain medical records from subjects' PCPs (when subject consent to do so had been obtained). For example:

- Subject (b) (6) (Study CLIN3102, placebo arm) was consented on (b) (6); a request for medical records was sent on Day 1 of dosing (b) (6)
- Subject (b) (6) (Study CLIN3103, difelikefalin arm) was consented on (b) (6) a request for medical records was faxed on (b) (6); first dose of study drug administered on (b) (6)

In Dr. Kumar's response to the inspection findings regarding his failure to acquire and review relevant medical records, he acknowledged the findings and acknowledged that he and his site staff were not aware of the existence of the medical record documents generated during hemodialysis. He plans to create a new SOP instructing staff to print and retain all subject records generated during hemodialysis and to develop a procedure to ensure the ongoing review of concomitant medications at each study visit.

Reviewer comments: Both study protocols require that the use of antipruritic medications be recorded on an ongoing basis starting at screening, and that no new medication to treat itch should be initiated during the studies. Study staff did not have access to all relevant HD electronic medical record (EMR) systems. Though the issue of missing HD records was mentioned by sponsor monitors in several monitoring visits, (exhibit 24 p 4), it was not remedied by the time of FDA's inspection, which discovered the additional EMR sources for HD records outside of study staff's awareness. Because of the failure to identify the administration of diphenhydramine during hemodialysis to Subject (b) (6) 16 times during the study, along with the additional evidence above regarding failures

to review or completely review dialysis records and other medical records for multiple study subjects, the study data generated by this site regarding concomitant medications is not reliable. No evidence of harm to subjects was identified related to the failures to acquire and review medical records. Dr. Kumar's preventive action plans seem adequate.

The endpoint worst-itch NRS data could not be verified for Subject (b) (6) (Study CLIN3102, difelikefalin arm) at three timepoints during Weeks 6 and 7. As shown in Figure 1 below, the source records for three dates are uninterpretable in terms of the subject's intended response. Additionally, in two of the cases (b) (6) and (b) (6) someone other than the subject initialed the response. The training manual for the patient-reported outcomes states that no one other than the subject is to write on the document in the area of the subject response.

Figure 1: Subject (b) (6) source endpoint worksheets

Source NRS documents reviewed for 7 (of 22) other subjects in Study CLIN3102 and for 9 of 13 subjects in Study CLIN3103 demonstrated no additional cases of ambiguous responses and no discrepancies with the submitted subject level line listings.

Reviewer comment: The study endpoint is based on the change in the worst-itch NRS from baseline at Week 12. Thus the ambiguous responses in Figure 1 would not impact the endpoint result for this subject or for the study. However, the failure of the CI to resolve the ambiguity in this case, the presence of input from someone other than the subject in the restricted response area of the source document, as well as the input of the lower NRS value of the ambiguous responses in all three cases raise concerns about how the endpoint data was collected at the site and thus the reliability of the endpoint data. Of note, the worksheets appear to have been completed at exactly (b) (6) AM.

Incorrect IP dosing was identified for three study subjects: (b) (6) (Study CLIN3103, difelikefalin arm), (b) (6) (Study CLIN3103, difelikefalin arm), and (b) (6) (Study CLIN3103, placebo arm), because of failure to follow the protocol in terms of dose calculation. IP dose was to be calculated based on the estimated dry weight (EDW) at screening, and the weight

was to be rounded down if needed. In the case of two of the study subjects, the IP dose was incorrectly calculated based on the EDW at study Day 1. For example, Subject (b) (6) (Study CLIN3103, difelikefalin arm) was incorrectly administered the study drug in a dose of 0.62 ml throughout the double-blind portion of the study; the correct dose should have been 0.61 ml. In the third case Subject (b) (6) (Study CLIN3103, placebo), the IP calculation was incorrectly based on the rounding up of subject weight.

The doses administered in all three cases were incorrect by less than 10%. The IP dose source record template at the site was developed by Dr. Kumar and his staff. The IP template contains the incorrect instruction to base the dose on the EDW at screening, instead of at Day 1 as specified in the protocol.

The protocol specified that IP administration was to be followed by a 10 ml saline flush in all cases in which the IP was administered after the conclusion of hemodialysis, after rinse back. Source records at the site demonstrate multiple instances in which IP was administered after the conclusion of hemodialysis and no saline flush was administered. The IP dose administration template at the site (developed by Dr. Kumar and his staff) includes incorrect administration instructions, stating that the saline flush should be given only if IP is administered with rinse back.

In Dr. Kumar's written response, he acknowledged the IP dosing errors and the errors in the template source worksheets. His preventive action plan includes the use of a second reviewer to check study specific site source templates to ensure that all instructions are as per protocol.

Reviewer comments: None of the documented errors regarding IP dose or IP administration technique appear to impact the studies' efficacy result, nor to have impacted subject safety. However, the repeated nature of the errors, and Dr. Kumar's failure to identify the root cause of these errors (incorrect templates) call in to question the adequacy of Dr. Kumar's supervision of the study.

Several study documents were found to be missing during the inspection as follows:

- For Study CLIN3102, the site did not maintain adequate documentation of certification for two study staff. The sponsor required that all study staff who will administer PROs or OROs train and complete a certification examination before administering the PROs. Delegation and training record shows 2 study coordinators: (b) (6) were delegated to PRO administration, but shows no date for protocol review, and no certification signature for (b) (6)
- For StudyCLIN3103, a Note to File from Dr. Kumar states training documentation and delegation log were lost for one of the dialysis centers. The NTF was to act as a stand-in documentation for the training that occurred on 6/17/2019 on IP preparation and administration; clinic staff names were included in the NTF.
- For Study CLIN3102, no information was included for one of the dialysis centers involved in the trial: not on Form 1572 , and not listed on sponsor-required satellite site oversight plan. Dialysis sites qualified as satellite sites and were required to be listed on the oversight plan.

CI Kumar acknowledges the observations above and has pledged to corrective actions including reinstituting staff training and ensuring proper documentation of training and certifications.

Reviewer Comment: Regarding the errors and omissions above, importantly, there was no evidence of patient harm. Though individual instances of the poor study conduct above do not constitute insurmountable challenges, their collective distribution across different contexts, the nature of these errors, and their persistence despite some being flagged by site monitors, call into doubt Dr. Kumar's supervision and the quality of the data being generated at this site.

In summary, the inspection at CI Kumar site revealed notable regulatory deficiencies and poor data quality across the totality of observations that centered on inadequate maintenance of case histories, evidence of unclear end point data collection and staff interference for at least 1 subject, and insufficient CI supervision. Based on the inspection findings and the insufficient quality of data from Dr. Kumar's site, we recommend conducting a sensitivity analysis by excluding the data generated by Dr. Kumar to assess the validity and robustness of the results from the primary analysis.

2. Ayesu, Kwabena
   7912 Forest City Road, Orlando, FL 32810
   Study: CR845-CLIN3103
   Site Number: 840007
   Date of Inspection:

   This inspection was conducted on-site. For study -CLIN3103, the site screened 47 subjects and enrolled and dosed 34 subjects. 3 subjects were terminated early and 31 subjects completed the study.

   There was no concern with maintenance of the blind. Source records were reviewed for primary and secondary efficacy data for 25 out of the randomized 34 subjects, and Informed Consent Forms were reviewed for all 47 screened subjects.

   Source records were all in paper form, and consisted of ICFs, medical histories, concomitant medications, adverse events, investigational product usage, lab results, progress notes, and NRS worksheets. No discrepancies were identified between the submitted data listing and source records.

   Several monitoring reports are noted to stress inclusion of HD flowsheets for 3 months prior to screening for all subjects, and that CI was to update the Investigator Source Agreement to indicate if flow sheets will be stored electronically.

   Reviewer comment: The scope of inspection did not include review of HD records to verify HD concomitant meds and AE data were captured, as there was no indication of a need for this at the time of inspection. As noted in the previous section under CI Kumar's inspection, we cannot rule out that missing HD records may have also impacted the capture of relevant concomitant medications at this CI site, but we do not have concrete evidence for this.

Overall, the inspection reveals likely adequate adherence to the regulations and the investigational plan. Data from this site appear acceptable in support of this NDA.

3. Awad, Ahmed
   3930 Washington Street, Kansas City, MO 64111
   Study: CR845-CLIN3102
   Site Number: 119
   Date of Inspection: 4/19/21-4/23/21

   This inspection was conducted on-site. For study -CLIN3102, the site screened 20 subjects and enrolled and dosed 19 subjects. 9 subjects were terminated early and 10 subjects completed the study.

   There were no major protocol deviations or any significant concern with maintenance of the blind. Source records were noted to be organized, accurate, original, complete, and legible. Source records were noted to include electronic medical records, HD records, study specific case report forms, laboratory results, progress and nursing notes, EKGs, dosing records, sample requisition forms, and Dr. Awad's review of the assessments.

   Primary and secondary endpoint data was verifiable for the study, and there was no evidence of under-reporting of SAE's/AE's.

   Reviewer comments: The scope of inspection did not include review of HD records to verify HD concomitant medication and adverse event data, as there was no indication of a need for this at the time of inspection.

   Overall, the inspection revealed adequate adherence to the regulations and the investigational plan. Data from this site appear acceptable in support of this NDA.

4. Sponsor: Cara Therapeutics, Inc.
   107 Elm St FL 9, Stamford, CT 06902-3834
   Studies: CR845-CLIN3102, CR845-CLIN3103
   Date of Inspection: 3/1/2021-3/5/2021

   This inspection was conducted on-site. The following were reviewed during the inspection: overview of the firm, monitoring and selection of clinical sites, investigators, and monitors; Forms FDA-1572; Data Safety Monitoring Board and the Independent Data Monitoring Committee charter and meeting minutes; handling of safety events; standard operating procedures; investigational plans; record retention; electronic database; and handling of test articles.

   Overall, the inspection revealed adequate adherence to the regulations and the investigational plan.

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M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: July 22, 2021

To: Kendall Marcus, M.D., Director
Division of Dermatology and Dentistry

Through: Dominic Chiapperino, Ph.D., Director
Chad Reissig, Ph.D., Supervisory Pharmacologist
Controlled Substance Staff

From: Katherine Bonson, Ph.D., Senior Pharmacologist
Controlled Substance Staff

Subject: Difelikefalin, under NDA 214916
KORSUVA, IV bolus 3 times per week (0.5 µg/kg per dose) sterile solution in a single use (b) (4) glass vials containing (b) (4)
IND 123140
Indication: Treatment of chronic kidney disease-associated pruritus (CKD-aP; uremic pruritus).
Sponsor: Cara Therapeutics, Inc.

Materials reviewed: NDA 214916 (submitted December 23, 2020)
Statistical review of human abuse potential study
(Wei Liu, Ph.D., Office of Biostatistics, April 14, 2021)
Statistical review of human physical dependence study
(Anna Sun, Ph.D., Office of Biostatistics, July 7, 2021)

TABLE OF CONTENTS

I. EXECUTIVE SUMMARY

1. Background

The Division of Dermatology and Dentistry (DDD) consulted the Controlled Substance Staff (CSS) to request an abuse potential assessment of the preclinical and clinical studies conducted with difelikefalin (previously known as CR845; tradename KORSUVA) under NDA 214916 (IND 123140), submitted by Cara Therapeutics, Inc.

Difelikefalin is a hydrophilic tetrapeptide (4-amino-1-((R)-6- amino-2-((R)-2-((R)-2-((R)-2-amino-3-phenylpropanamido)-3-phenylpropanamido)-4-methylpentanamido)-hexanoyl)piperidine-4-carboxylic acid that acts as a full kappa opioid agonist. Its abbreviated peptide sequence is D-Phe-D-Phe-D-Leu-D-Lys-[ɣ(4-N- piperidinyl) amino carboxylic acid], acetate salt.

Difelikefalin is proposed for the treatment of chronic kidney disease-associated pruritus (CKD-aP; also known as uremic pruritus). The drug product is formulated as a solution for intravenous administration (b) (4) ml) and is intended to be administered as an IV bolus (0.5 µg/kg per dose) 3 times per week, following the patient's hemodialysis session. (b) (4)

There are currently no FDA-approved drug products for the treatment of CKD-aP. Difelikefalin received Breakthrough status in 2017 and is requesting a Priority Review for this NDA.

The physiochemical properties of difelikefalin (e.g., hydrophilic, synthetic D-amino acid peptide with high polar surface area and charge at physiological pH) minimizes passive diffusion or active transport across membranes, thus restricting penetration into the brain. Pharmacokinetic studies showed that difelikefalin was not detectable in the brain, which should limit its likelihood of having abuse potential.

The Sponsor claims that the drug's limited membrane permeability through passive diffusion limits its central nervous system (CNS) penetration. In animals, a 160 μg/kg dose of difelikefalin produced no detectable brain penetration, despite plasma levels of the drug that were >120-folder greater than those produced by the therapeutic dose.

However, the psychiatric adverse events observed in Phase 1 and Phase 2 clinical studies, which include dizziness, somnolence, paraesthesia, and hallucinations, suggest that the drug has CNS activity. Serious physiological adverse events include tachycardia and increases in blood sodium as a result of the aquaretic effect of difelikefalin (i.e., an increase in free water elimination resulting in low urine osmolality).

(b) (4)

In the NDA, the Sponsor concludes that difelikefalin has no significant abuse potential and should not be recommended for scheduling under the Controlled Substances Act (CSA). This conclusion is based on the Sponsor's conclusion that animal and human abuse-related studies showed no positive signals for abuse potential. Additionally, the Sponsor concludes that, "The restricted access of difelikefalin to healthcare professionals in specialized clinics (i.e., dialysis providers) will minimize the potential for diversion, theft, or loss of difelikefalin. Furthermore, potential abuse of the marketed formulation via the IV route would be limited by the volume required to inject a supratherapeutic dose such as the ones administered in the human abuse potential study (i.e., a 5 and 15 μg/kg [10 and 30 times therapeutic]] for a 70 kg individual would require 7 to 21 mL of solution). Drugs of abuse have strong dose-response functions. The results from this study also revealed that increasing the dose of difelikefalin to 15 μg/kg did not increase the small drug liking signal, further demonstrating its lack of abuse potential."

2. Conclusions

CSS has reviewed the nonclinical and clinical abuse-related data submitted in NDA 214916 for difelikefalin and concludes that the drug has no significant abuse potential and should not be recommended for scheduling under the CSA. This conclusion is based on the data described below:

- Difelikefalin is a peptide that does not have a chemical structure that is similar to other drugs controlled under the CSA.

- In receptor binding and functional studies, difelikefalin has highly selective activity at kappa opioid receptors as an agonist.

- In animal pharmacokinetic studies, difelikefalin produced very low brain penetration. Although this should restrict its ability to produce CNS effects, difelikefalin administration to humans produced sedation, somnolence, and fatigue. This shows that difelikefalin is CNS-active and therefore not limited to peripheral activity.

- In a general behavior test in rats, difelikefalin produced dose-dependent decreases in locomotion and muscle coordination.

- The animal abuse-related studies (drug discrimination, self-administration, conditioned place preference, and physical dependence) are not interpretable because they all use inappropriate doses of difelikefalin that are many-fold greater than the acceptable dose range recommended in the 2017 FDA guidance for industry: *Assessment of the Abuse Potential of Drugs.* The Sponsor did not submit the protocols for these studies to CSS prior to study initiation. Thus, these studies cannot inform the abuse potential assessment of difelikefalin.

- In a human abuse potential study with subjects experienced with opioids and psychedelics, difelikefalin did not produce meaningful signals of abuse potential on positive subjective measures such as VAS for Drug Liking, Overall Drug Liking, Good Drug Effects, High, or Take Drug Again. On the VAS for Drug Similarity, difelikefalin did not produce scores of similarity for major classes of drugs of abuse, including benzodiazepines, cannabinoids, hallucinogens, opioids, or stimulants. Difelikefalin did not produce increases on the Hallucinogen Rating Scale, demonstrating it does not produce psychedelic effects. On the Price Value Assessment, difelikefalin was rated as having a low monetary value compared to pentazocine. There were no changes in pupil size compared to placebo. None of the adverse events produced by difelikefalin included euphoria or hallucinations. These data suggest that difelikefalin does not have abuse potential.

- An assessment of abuse-related adverse events in Phase 1 and Phase 2/3 studies showed no meaningful signals for euphoria or hallucinations. However, there were CNS-related AEs including sedation, somnolence, and fatigue (all at a rate >1%). This demonstrates that difelikefalin has centrally-mediated effects and should not be classified as a drug that is restricted to peripheral activity.

3. Recommendations

CSS has determined that difelikefalin does not have abuse potential and recommends that:

- Difelikefalin should not be recommended for scheduling under the CSA.

- If approved, the difelikefalin [redacted] (b) (4)

II. DISCUSSION

1. Chemistry

1.1 Drug Substance

Difelikefalin is a new molecular entity identified by CAS registry number: 1024828-77-0. Chemically, difelikefalin is a hydrophilic tetrapeptide: 4-amino-1-((R)-6- amino-2-((R)-2-((R)-2-((R)-2-amino-3-phenylpropanamido)-3-phenylpropanamido)-4-methylpentanamido)-hexanoyl)piperidine-4-carboxylic acid. Its abbreviated peptide sequence is D-Phe-D-Phe-D-Leu-D-Lys-[ɣ(4-N- piperidinyl) amino carboxylic acid], acetate salt. It has a molecular formula of $C_{36}H_{53}N_7O_6$ and a molecular weight of 679 [redacted] (b) (4) It is freely soluble in water.

1.2 Drug Product

The drug product is a sterile solution in a single use [redacted] (b) (4) glass vials containing [redacted] (b) (4) mL of peptide in 0.04M isotonic acetate buffer, pH 4.5 (composed of acetic acid, sodium acetate trihydrate, sodium chloride, and water, [redacted] (b) (4) It is ready-to-use through withdrawal of the solution into an intravenous syringe.

2. Nonclinical Abuse-Related Studies

2.1 Receptor Binding and Functional Studies (Study # CR845-PHARM001, CR845-PHARM003, CR845-PHARM004, CR845-PHARM071, CR845-PHARM091, and CR845-PHARM092)

In a series of receptor binding studies, difelikefalin was found to have high affinity for kappa opioid receptors (KORs) in humans (Ki = 0.32 nM). When difelikefalin was tested at 123 targets (88 receptors, 18 ion channels, 7 enzymes, and 5 transporters, at a concentration of 10 µM, difelikefalin only displaced radioligand binding by >50% at kappa opioid receptors. The sites tested included abuse-related sites such as dopamine (D1-D5), serotonin (1A, 1B, 2A, 2B, 2C, 3, 5A, 6, and 7), opioid (mu, kappa, and delta), cannabinoid (CB-1 and CB-2), nicotine, GABA (A, B, and benzodiazepine), glutamate (AMPA, phencyclidine, glycine, kainate), sigma (1 and 2), and transporters (dopamine, serotonin, norepinephrine, and GABA).

An *in vitro* functional assay was then conducted using a cyclic adenosine monophosphate (cAMP) production assay with mouse KOR and using a reporter gene assay with human KOR. For the cAMP assay in mice, difelikefalin was a highly potent ligand in producing 50% of the maximal response (EC_{50}) at a concentration of 0.048 nM with 96% efficacy. Similarly, for the reporter gene assay in humans, difelikefalin was a highly potent ligand with an EC_{50} of 0.16 nM and 99% efficacy. When the reporter gene assay was also conducted with human mu and delta

opioid receptors (MORs and DORs) at concentrations of difelikefalin up to 10,000 nM, there was no functionality detected.

These data show that difelikefalin is a highly-selective, full and potent agonist at rodent and human KORs with no functional activity at MORs or DORs or other abuse-related sites.

2.2 Animal Behavioral Studies

a. General Behavioral Observations

i. Rat Irwin Test (Study # CR845-SP055), Locomotion Test (Study # SBL069-129), and Rotorod Test (Study # SBL069-130, CR845-SP033, CR845-SP034)

In an Irwin study conducted in rats (10 rats/sex/group) during a toxicity study, difelikefalin was administered intravenously at doses of 0, 1, 5, and 25 mg/kg. A functional observational battery (FOB) assessment was conducted 2 and 24 hours after drug administration. It is unclear why immediate observations were not scheduled following intravenous administration of the drug, but CSS did not review the protocol prior to study to provide feedback on the study design. The FOB included assessment of behavior (observational, autonomic, neuromuscular, and sensorimotor functioning) while animals were in the home cage, upon removal of animals from the home cage, and during placement of animals in an open field cage.

At the first observations at the 2 hour time point, each dose of difelikefalin produced non-dose dependent home cage and open field reductions in general activity and rearing behavior, as well as changes in body posture that included flattening, hunching, Straub tail, and leaning on the cage wall or on its forelimbs. Additional changes included miosis, lacrimation, and increases in urination. By the following day at the 24 hour observation time point, these behaviors had returned to normal.

During a study evaluating locomotor behavior in mice, difelikefalin produced a dose-dependent reduction in movement around the test cage. Difelikefalin produced no effects on locomotion at doses of 0.03 and 0.1 mg/kg, but did produce reductions at doses of 0.3, 1.0, and 3.0 mg/kg

Similarly, during studies in which the forepaws of mice and rats are placed on a slowly rotating rod that is suspended above the cage floor, difelikefalin dose-dependently produced a loss of grip strength on the rotorod after a short period, indicating a reduction in motor coordination. This occurred at doses of 1.0, 3.0, and 10 mg/kg, but not at doses of 0.1 and 0.3 mg/kg.

ii. Behavioral Observations During Animal Toxicology Studies (Study # CR845-TOX044, SBL069-078, SBL069-104, CR845-TOX045, SBL069-076, SBL069-103, CR845-TOX085, CR845-TOX214, CR845-TOX219, CR845SP040)

Administration of difelikefalin in single-dose and repeat-dose animal toxicology studies produced similar behavioral observations as those reported in the Irwin test (above). Rats received difelikefalin at doses ranging from 0.25 to 50 mg/kg/day (i.v.) for time periods ranging from 28 days up to 26 weeks. Monkeys received difelikefalin at doses ranging from 0.06 to 1 mg/kg/day in 13- and 39-week studies, and at doses up to 4 mg/kg/day in a 4-week study.

In these rat and monkey studies, difelikefalin produced dose-dependent behavioral observations that included decreased spontaneous activity and general responsiveness, lethargy, ataxia, foreleg abduction, altered posture, eyes partially closed/sunken. Resolution of the behavioral effects occurred between 3 to 7 days after difelikefalin administration began, suggesting the development of tolerance. There were additional transient observations of weight loss, decreased body weight gain, lower body weight, and reduction in water/food consumption.

iii. Behavioral Observations During Respiratory Safety Study (Study #CR845SP040)

In a rat respiratory safety study, difelikefalin produced minimal decreases in respiratory rate and minimal increases in tidal volume at doses above the no observed adverse effect level (NOAEL) of 25 mg/kg, a dose that represents a 8000-fold multiple of the C_{max} human exposure at the proposed clinical dose of 0.5 μg/kg. The Sponsor interprets these data as suggesting "that the rats were capable of compensating for the decreased respiratory rate through a compensatory physiological increase in tidal volume."

Thus, unlike mu opioid agonists, difelikefalin does not appear to produce a reduction in respiration that could lead to death in the case of overdose.

b. Abuse-Related Behavioral Studies

In April 2015, CSS informed the Sponsor that we were available to provide feedback on the design of the self-administration, drug discrimination, and physical dependence studies in animals. However, these studies were initiated and completed without prior CSS feedback.

In September 2017, we informed the Sponsor that we would waive the requirements to use both male and female animals in preclinical studies, and to conduct these studies under Good Laboratory Procedures (GLP), since they had already completed the preclinical studies.

Later in September 2017, the Sponsor asked for confirmation that these three animal abuse studies were adequate to characterize abuse potential. We reiterated that since the Sponsor had declined our offer to provide feedback on the study protocols, the adequacy of these studies would be a review issue following submission of the NDA. We also emphasized that we would need pharmacokinetic information regarding the plasma levels produced by each dose via the route of administration used in the study in order to evaluate the appropriateness of the study design.

In the NDA, the Sponsor provided the following methodology for dose selection:

> Dose selection for the conditioned place preference study was based on extrapolation from prior pharmacokinetic studies in rats.
>
> Doses for the drug discrimination and self-administration studies were based on dose finding studies to identify doses that were not impairing performances.

The studies were conducted in rats using the IV route of administration, as this is the clinically intended route of difelikefalin administration for the current indication and it results in rapid delivery of the drug, with T_{max} observed within 5 minutes postdose.

(b) (4)

[redacted]

These methods of dose selection are not aligned with those that are recommended in the 2017 FDA guidance for industry: Assessment of Abuse Potential of Drugs ("the 2017 guidance"). In that FDA guidance, it is recommended that doses for animal abuse potential studies produce plasma levels that are similar to and 2-3 times greater than (for drug discrimination, conditioned place preference, and physical dependence studies) or less (for self-administration studies) than those produced by the propose therapeutic dose in humans.

i. Drug Discrimination Study with Difelikefalin (Study #CR845-TOX-079)

Drug discrimination is an experimental method of determining whether a test drug produces physical and behavioral responses that are similar to a training drug with specific pharmacological effects. Any centrally-acting drug can serve as the training drug. When the training drug is a known drug of abuse, drug discrimination in animals serves as an important method for predicting whether the effects of a new drug will similarly have abuse potential. Drugs that produce a response similar to known drugs of abuse in animals are also likely to be abused by humans.

In drug discrimination, an animal learns to press one bar when it receives the training drug and another bar when it receives a placebo. Once responding to the training drug and placebo is stable, an animal is given a challenge session with the test drug. A test drug is said to have "full generalization" to the training drug when the test drug produces bar pressing ≥80% on the bar associated with the training drug.

Critical Evaluation of Methodology

The protocol for this drug discrimination study was not reviewed by CSS prior to its initiation and the first time the completed study report has been submitted is in the present NDA. There are numerous problems with the design of this study based on inconsistencies with the procedures recommended in the 2017 guidance, as follows:

- The doses of difelikefalin were selected on the basis of preventing behavioral impairment, instead of being based on plasma levels equivalent to and up to 3-fold greater than those produced in humans by the proposed therapeutic dose.

- The intravenous doses of difelikefalin that were used in this study (0.05–0.5 mg/kg) produced plasma levels that were up to 421-fold greater than those produced in humans by the proposed therapeutic dose, instead of ranging up to 3-fold greater. When extremely high doses of a drug are administered, the pharmacology of the drug becomes much less specific. Thus, receptor systems that normally would not be activated at lower doses can become pharmacologically relevant. This can change the interoceptive cue of that drug so dramatically that it no longer will generalize to another drug in its class.

- The study used a fixed ratio FR5 schedule of reinforcement, instead of the recommended FR10.

- Full generalization was defined as 75% accuracy on the drug-associated lever, instead of the recommended 80% accuracy.

- Animals were rewarded during test sessions following lever selection, instead of removing animals from the test cage after selection.

These methodological deviations from the 2017 guidance, especially the inappropriate dose selection, make this study uninterpretable.

Thus, it is not possible to conclude from this study whether difelikefalin produces an interoceptive cue that is similar or dissimilar to that of (-)pentazocine.

Method

Female rats (n = 6-10/treatment) were trained to discriminate intraperitoneally-administered (-)-pentazocine (5.0 mg/kg) from vehicle. The Sponsor justifies using female rats because they are "smaller and weight stable as adults" and justifies using the intraperitoneal route IP route because it combines good bioavailability and ease of dosing. Pentazocine is a kappa opioid agonist that has a mechanism similar to difelikefalin. During training, the schedule of reinforcement was gradually raised from fixed ratio (FR) 1 to FR5. Full generalization was defined as 75% accuracy on the drug-associated lever.

In the test sessions, difelikefalin, (-)-pentazocine and the "reference comparator," butorphanol (a kappa opioid agonist and mu opioid partial agonist), were given by the IV route because it is the clinical route of administration of difelikefalin in humans.

As noted above, the doses of difelikefalin and (-)-pentazocine were selected following a dose-finding study that identified doses that would not impair performance. The protocol states that "doses of butorphanol were selected based on 'in house' experience at (b) (4)."

The test sessions were 10 minutes in duration. Usually, during the first 2.5 minutes, animals were not rewarded for their lever selections, but were rewarded with sweetened milk rewards during the final 7.5 minutes for pressing either lever. However, according to the protocol, only the results from the 2.5 minutes non-rewarded part of the test were used in the drug-discrimination assessment. In the 2017 Guidance, we state that, "Animals are not typically rewarded during challenge sessions in order to maintain appropriate associative training."

Results

The results from this study will be summarized only briefly, given that the data for difelikefalin are uninterpretable.

During test sessions, intravenously administered (-)-pentazocine (0.017–0.5 mg/kg) and butorphanol (0.001-0.25 mg/kg) dose-dependently generalized to the training drug, (-)-pentazocine, which was administered intraperitoneally during training sessions.

In contrast, intravenously administered difelikefalin (0.05–0.5 mg/kg) produced partial generalization to the vehicle cue (≤ 35%) only at the 0.125 mg/kg) dose. This dose of difelikefalin produces plasma levels that are 280 times greater than those produced in humans at the proposed therapeutic dose. However, as noted above, the doses tested are too high and no conclusions can be drawn about the similarity of difelikefalin to (-)pentazocine.

Conclusions

It is not possible to interpret this study, given the serious protocol design flaws. Specifically, the lack of an abuse signal in this study is likely an artifact of the poor design, rather than evidence that difelikefalin does not produce an interoceptive cue that generalizes to another kappa opioid agonist.

ii. Self-Administration Study in Rats with Difelikefalin (Study #CR845-TOX081)

A self-administration study evaluates whether a test drug has rewarding properties that are sufficient to produce reinforcement (i.e., the likelihood that an animal will repeatedly self-administer the test drug after initial exposure). Animals are first trained to press a bar in the test cage in order to receive a food reward. After animals consistently bar-press in response for food, they begin to receive an intravenous dose of a known drug of abuse (training drug) as the reward, instead of food. They are also tested with vehicle to ensure that bar-pressing is not maintained for a substance without rewarding properties. Once animals stably bar-press (self-administer) the training drug, they are then allowed to self-administer intravenous doses of the test drug. If the test drug produces a high level of self-administration compared to vehicle, there is a good probability that the drug will produce rewarding properties in humans that are supportive of drug abuse.

Critical Evaluation of Methodology

The protocol for this self-administration study was not reviewed by CSS prior to its initiation and the first time the completed study report has been submitted is in the present NDA. There are numerous problems with the design of this study based on inconsistencies with the procedures recommended in the 2017 guidance, as follows:

- The doses of difelikefalin were selected on the basis of preventing behavioral impairment, instead of being based on fractions of plasma levels produced in humans by the proposed therapeutic dose. The Sponsor is aware of this discrepancy, because they state in the NDA submission that, "While doses in the self-administration study in particular were higher than those expected based on the more recent recommendations provided in the final 2017 FDA Guidance, the doses selected were appropriate because they did not produce significant behavioral impairments."

- The intravenous doses of difelikefalin that were used in this study (0.05–0.5 mg/kg) produced plasma levels that were up to 94-fold greater than those produced in humans by the proposed therapeutic dose, instead of using doses that produce fractions of the human therapeutic plasma levels.

- The study used a fixed ratio FR5 schedule of reinforcement, instead of the recommended FR10.

In self-administration, animals work (bar-press) to obtain repeated small doses of a rewarding drug, which over time accumulate to produce a rewarding sensation that increases with continued bar-pressing. These small doses are typically fractions of the doses that produce plasma levels equivalent to those produced by the human therapeutic dose. If a single dose that is used in an animal self-administration study immediately produces the desired rewarding effect, animals will satiate after a few infusions and will fail to continue to bar-press for the drug.

Since the doses of difelikefalin used in this self-administration study ranged from 1-fold to 94-fold of the human therapeutic dose, it is not possible to determine whether the failure of rats to self-administer these doses represents a lack of rewarding properties of the drug, or instead satiation of animals from the high doses.

Methods

Male rats (n = 5-8/dose) were initially trained to press a lever to receive heroin (0.015 mg/kg/infusion, i.v.), using a fixed ratio (FR)5 final schedule of reinforcement. Once responding for heroin was stable, animals were allowed to lever press to receive a range of doses of difelikefalin (0.001, 0.005, 0.025, and 0.125 mg/kg/infusion, i.v.), (-)pentazocine (the positive control; 0.03, 0.1, and 0.245 mg/kg/infusion), or vehicle (i.v.) in each session. According to the protocol, "doses of (-)-pentazocine and heroin were selected based on previous experience in intravenous self-administration studies in rats. The maximum dose of (-)-pentazocine was limited by its solubility."

Animals were allowed access to each treatment for a maximum of 20 injections per 2-hour session each day under an FR5 schedule of reinforcement. Animals were tested once per day for 5 to 6 days per week. Each drug dose was tested in 4 sessions. Each animal received a non-contingent administration of the drug at the start of each session, in order to pique interest in the drug.

As expected, heroin produced a high degree of self-administration (~17 infusions/session at doses of 0.015 mg/kg/infusion), while vehicle produced a low degree of self-administration (~4 infusions/session). The positive control, (-)-pentazocine produced a moderate degree of self-administration (~8 to 12 infusions/session).

Difelikefalin (0.001, 0.005, 0.025 or 0.125 mg/kg/injection) produced self-administration at each dose that was similar to that of saline (<6 infusions/session). However, based on a pharmacokinetic evaluation, the plasma levels produced by these rat doses of difelikefalin are equivalent to plasma levels in humans that range from ~1-fold to 94-fold for the proposed therapeutic dose.

Conclusions

It is not possible to interpret this study, given the serious protocol design flaws. Specifically, the lack of an abuse signal in this study is likely an artifact of the poor design, rather than evidence that difelikefalin does not produce rewarding effects indicative of abuse potential.

iii. Conditioned Place Preference (Study #SP036)

A conditioned place preference (CPP) study evaluates whether a test drug produces rewarding effects that are demonstrated by an animal's preference to be on the side of a cage where it received the test drug, as opposed to the side where it received vehicle. Notably, CPP differs from self-administration in that it does not measure whether the rewarding effects of a drug produce reinforcement. It is also not considered to be as sensitive or reliable as self-administration.

Critical Evaluation of Methodology

The protocol for this CPP study was not reviewed by CSS prior to its initiation and the first time the completed study report has been submitted is in the present NDA. There are numerous problems with the design of this study based on inconsistencies with the procedures recommended in the 2017 guidance, as follows:

- The doses of difelikefalin were selected on the basis of "extrapolation from prior pharmacokinetic studies in rats," instead of being based on plasma levels equivalent to, and up to 3-fold greater than those produced in humans by the proposed therapeutic dose.

- The intravenous doses of difelikefalin that were used in this study (0.32 to 3.2 mg/kg) produced plasma levels that ranged from 201-fold to 2452-fold greater than those produced in humans by the proposed therapeutic dose. When extremely high doses of a

> drug are administered, the pharmacology of the drug becomes much less specific. Thus, receptor systems that normally would not be activated at lower doses can become pharmacologically relevant. This can change the properties of that drug so dramatically that it no longer will be experienced as rewarding to an animal.

These methodological deviations from the 2017 guidance, especially the inappropriate dose selection, make this study uninterpretable.

Thus, it is not possible to conclude from this study whether difelikefalin produces rewarding properties that would induce CPP.

Methods

The methods for the CPP study are provided **verbatim** from the protocol, given the complexity of the procedures that were conducted:

"A non-biased place conditioning protocol was used for all assessments. During the pre-conditioning phase, drug-naïve rats were placed in the middle of the central area and had free access to all compartments of the apparatus for 20 minutes. They were then assigned to 1 compartment for drug conditioning and to 1 of the 6 treatment groups. The assignments to the putative side of conditioning were equally balanced between a black and a white compartment for all groups.

"During the conditioning sessions, the animals (n=10-14/group) were placed into the conditioning chamber for 30 minutes immediately following dosing. Rats were subjected to either two 2-day (Test 1) or 4-day (Test 2) cycles. Each cycle consisted of 1 drug conditioning day and 1 vehicle (alternate compartment) conditioning day. On the test day, rats (drug-free) were placed into the apparatus and had access to all compartments for 20 minutes and the relative proportion of time spent in each compartment was measured.

The results show that the mu opioid agonist, morphine (3.2 mg/kg, i.v.), induced a significant place preference when compared to vehicle.

The kappa opioid agonist, U50,488H (3.2 mg/kg, i.v.) produced a conditioned place aversion when compared to vehicle.

Difelikefalin (0.32 to 3.2 mg/kg, i.v.) did not produce a place preference or aversion when compared to vehicle."

Conclusions

It is not possible to interpret this study, given the serious protocol design flaws. Specifically, the lack of an abuse signal in this study is likely an artifact of the poor design, rather than evidence that difelikefalin does not produce rewarding effects indicative of abuse potential.

2.3 Physical Dependence Studies in Animals

a. Rat Physical Dependence Study with Difelikefalin (Study CR845-TOX080)

A physical dependence study was conducted in rats to determine if chronic administration of difelikefalin produces a withdrawal syndrome upon drug discontinuation, compared to morphine and vehicle.

Critical Evaluation of Methodology

The protocol for this rat physical dependence study was not reviewed by CSS prior to its initiation and the first time the completed study report has been submitted is in the present NDA. There are numerous problems with the design of this study based on inconsistencies with the procedures recommended in the 2017 guidance, as follows:

- The dose of difelikefalin was based on tolerability findings from a prior 28-day rat toxicity study, instead of being based on plasma levels equivalent to and up to 3-fold greater than those produced in humans by the proposed therapeutic dose.

- Only a single dose of difelikefalin was tested, instead of using several doses.

- The intravenous dose of difelikefalin that was used in this study (5.0 mg/kg) produced plasma levels that were 4331-fold greater than those produced in humans by the proposed therapeutic dose. When extremely high doses of a drug are administered, the pharmacology of the drug becomes much less specific. Thus, receptor systems that normally would not be activated at lower doses can become pharmacologically relevant. This can change the properties of that drug so dramatically that compensatory mechanisms may obviate any signs of withdrawal that might have emerged if lower doses had been tested.

- The routes of administration for the positive control (morphine) and difelikefalin are different (orally twice a day and intravenously once a day, respectively), instead of being given by the same route and schedule of administration. Since plasma levels of drug vacillate greatly between these two methods of drug administration, it is likely that there would be differences in the timing of behavioral changes following drug discontinuation.

These methodological deviations from the 2017 guidance, especially the inappropriate dose selection, make this study uninterpretable.

Thus, it is not possible to conclude from this study whether difelikefalin produces physical dependence in rats.

Methods

The physical dependence study was conducted in 4 groups of rats (n = 10-15/group) that received oral morphine, intravenous difelikefalin, and vehicle (both orally and intravenously). Animals received each treatment for 28 days, followed by a 7-day discontinuation period.

The positive control morphine was administered orally at a dose of 30 mg/kg BID (60 mg/kg/day). The oral route of administration for morphine was justified based on its used to validate the study methodology. In contrast, difelikefalin was administered intravenously, at an initial dose of 25 mg/kg, based on tolerability findings from a prior 28-day rat toxicity study. Dosing was stopped for 6 days after animals showed unacceptable reductions in body weight and feeding. Difelikefalin administration was then reinitiated intravenously at a dose of 5 mg/kg. This dose produces a plasma level that is 4331-fold greater than that produced in humans at the proposed therapeutic dose.

At the conclusion of the drug administration period, animals were discontinued from treatment and observed for 7 days. This duration is appropriate since the half-life of difelikefalin ranges from 2.7 to 5.5 hours in rats and animals should be observed for at least 5 half-lives (up to ~27 hours).

Results

Morphine-treated animals produced classic opioid withdrawal effects during the discontinuation period, compared to vehicle. These effects included jumping, wet dog shakes, irritability, decreases in body temperature and body weight, aggression and
anxious behaviors.

Difelikefalin-treated animals did not show any changes compared to vehicle during the discontinuation period.

Conclusions

It is not possible to interpret this study, given the serious protocol design flaws. Specifically, the lack of an abuse signal in this study is likely an artifact of the poor design, rather than evidence that difelikefalin does not produce physical dependence following chronic administration.

<u>b. Evaluation of Withdrawal Behaviors in Toxicology Studies (Study #SBL069-078; SBL069-104; CR845-TOX044; SBL069-076; SBL-069-103; CR845-TOX045; CR845-TOX085)</u>

During animal toxicology testing, difelikefalin was administered to rats and monkeys for up to 9 months at doses that produced plasma levels that were 500-fold to 4000-fold greater than exposures at the proposed therapeutic doses. Following drug discontinuation, animals were observed for withdrawal signs indicative of the development of physical dependence.

Although there were no withdrawal-like behaviors observed in these animals, these data are not interpretable because of the extremely high doses of difelikefalin administered. As noted above

in the dedicated rat physical dependence study, When extremely high doses of a drug are administered, the pharmacology of the drug becomes much less specific. Thus, receptor systems that normally would not be activated at lower doses can become pharmacologically relevant. This can change the properties of that drug so dramatically that compensatory mechanisms may obviate any signs of withdrawal that might not have emerged if lower doses had been tested.

3. Pharmacokinetics of Difelikefalin in Animals and Humans

a. Evaluation of Metabolites (Study # CR845-DMPK216, CR845-DMPK090, CR845-DMPK025, CR845-DMPK023, PBC069-127, PBC069-122, PBC069-094, PBC069- 082, PBC069-085, PBC069-086, PBC069-089, SBL069-132)

Metabolism studies show that difelikefalin does not undergo meaningful metabolism in animals or humans (including both healthy individuals and patients). Thus, difelikefalin does not produce any major metabolites in any species tested that would need evaluation for abuse potential.

b. Pharmacokinetic Parameters (Study # CR845-DMPK016, CR845-DMPK018, CR845-DMPK205, CR845-DMPK206, CR845-CLIN1001)

Difelikefalin produced dose-proportional increases in plasma levels when the drug was intravenously administered at doses from 0.3 to 3.0 mg/kg over 5 minutes to rats and monkeys. The time to maximum drug concentrations (Tmax) was very short (within 5 minutes following drug administration), as would be expected with the intravenous route. In monkeys, the half-life was 1.2 hours, while the half-life in rats was 5.5 hours.

In humans, difelikefalin also produced dose-proportional increases in plasma levels following intravenous administration at doses ranging from 2 to 40 μg/kg. The half-life of difelikefalin is ~2-3 hours in both healthy individuals and in renal patients. Approximately 90% of difelikefalin is eliminated in humans as unchanged drug in urine.

c. Brain Permeability (Study #CR845-DMPK028, CR845-DMPK060, CR845-DMPK061, CR845-DMPK078, CR845-DMPK093, CR845-DMPK095, CR845-DMPK210).

i. In vivo *studies*

Through *in vitro* studies using MDCKII and MDR1-MDCKII cellular monolayers (which have been used as a predictors of blood-brain barrier (BBB) permeability), it was shown that difelikefalin has low membrane permeability, even at concentrations that were greater than 1000-fold higher than those produced in humans at the proposed therapeutic dose.

In addition, human efflux and uptake transporters were tested with difelikefalin, but the drug was not a substrate or inhibitor of any of these sites.

ii. Whole Animal Studies (Study # PBC069-087, PBC069-088, PBC069-089, PBC069094, PBC069-122, CR845-DMPK016, CR845DMPK212, CR845-TOX043)

Radioactive difelikefalin is not detectable or is poorly distributed to the brain in rats (as evaluated with quantitative whole-body autoradiography and tissue dissection studies) and monkeys (as evaluated with qualitative autoradiography study) at plasma concentrations ranging from 400-fold to 1600-fold greater than human plasma levels produced by the proposed human dose.

This suggests that difelikefalin is a peripherally-acting drug that would not have central nervous system (CNS) effects in humans. However, as shown in Section 4.2, the CNS adverse events reported at a rate of >2% in clinical studies include sedation, somnolence, and fatigue.

4. Clinical Abuse-Related Studies with Difelikefalin

4.1 A Randomized, Single-Dose, Double-Blind, Active- and Placebo-Controlled, 4-Way Crossover Study to Assess the Relative Abuse Potential of Intravenous CR845 in Healthy, Recreational Polydrug Users (Study #CR845-CLIN1006)

This was a single-center, randomized, double-blind, active- and placebo-controlled, 4-way crossover human abuse potential (HAP) study assessing the abuse potential of difelikefalin in non-dependent, recreational opioid users. There was both a Qualification Phase and a Treatment Phase. Subjects resided on the clinic ward for the duration of the 14-day study, starting at the initiation of Qualification Phase procedures.

However, the 15 µg/kg i.v. dose of difelikefalin used in this HAP study is 30-fold greater than the therapeutic dose proposed for the treatment of uremic pruritus associated with chronic kidney disease (0.5 µg/kg, i.v.). Thus, this dose of difelikefalin is 10 times greater than the highest recommended dose for a HAP study (3-fold greater than the highest proposed therapeutic dose, based on the 2017 Guidance). According to the study report, the plasma levels produced by this dose are 29-fold greater than the plasma levels produced by the therapeutic dose.

Similarly, the 5 µg/kg i.v. dose of difelikefalin is 10-fold greater than the proposed therapeutic dose for the treatment of uremic pruritus associated with chronic kidney disease (0.5 µg/kg, i.v.), which is also 10 times greater than the lowest recommended dose for a HAP study (which should be the highest proposed therapeutic dose, based on the 2017 Guidance). According to the study

report, the plasma levels produced by this dose are 11-fold greater than the plasma levels produced by the therapeutic dose.

Although these doses are not ideal for a HAP study, they do provide information regarding whether very high doses produce rewarding responses. They also provide a characterization of adverse events at such high doses, including the development of serious adverse events.

Subjects

Subjects were 80% male and 86% white, with an average age of 28 years old (range: 19-55 years old).

A total of 69 subjects passed the Naloxone Challenge Test and entered the Qualification Phase. From this pool, 44 subjects entered the Treatment Phase and 39 subjects completed the Treatment Phase. Five of the 44 subjects were discontinued: 3 subjects left the study because of AEs (2 who received difelikefalin experienced anxiety or injection site phlebitis and 1 who received pentazocine experienced muscle spasms), and 2 withdrew consent.

Inclusionary and Exclusionary Criteria

Inclusionary criteria are standard, but include the following specific criteria to ensure that subjects:

- Have a current history of opioid use for non-therapeutic purposes on at least 10 occasions within the last year and at least once in the past 12 weeks.

- Are not currently physically dependent on opioids, as determined by the Naloxone Challenge Test.

- Have a current history of hallucinogen use (including LSD, psilocybin, mescaline, MDMA, *Salvia divinorum*, ketamine, and PCP) within the past 60 days. The Sponsor notes that this FDA-recommended criterion was submitted to them after enrollment of all subjects, so it could not be applied directly. However, 94% of men and 100% of women in the study conformed to this criterion.

Exclusionary criteria are also standard, but include the following specific criteria for issues related to drug abuse or psychiatric disorders:

- Subject had a history or current diagnosis of substance dependence (except nicotine and caffeine) or alcohol abuse, according to DSM-IV-TR criteria.

- Subject used prescription medication (except hormonal contraceptives), over-the-counter (OTC) medication (except acetaminophen), herbal supplements, or nutraceuticals within 48 hours prior to check-in to the Qualification Phase (Day 0) or anytime during the study.

- Subject had a history or presence of clinically significant neurologic or psychiatric disease.

- Subject had a positive alcohol breathalyzer test at screening or check-in to the Qualification Phase (Day 0).

- Subjects who had a positive urine drug screen (UDS) at screening or check-in to the Qualification Phase (Day 0) with the following exceptions: positive UDS for tetrahydrocannabinol (THC) at the Screening visit or check-in (Day 0) were allowed and positive UDS for opiates at the Screening visit only were allowed.

- Subjects who were heavy smokers who were unwilling to refrain from using prohibited tobacco-containing products or nicotine-containing products during the in-clinic phase of the study (and who were unwilling to refrain from cigarettes within 1 hour prior to dosing and within 4 hours following dosing.

Naloxone Challenge Test

An initial dose of naloxone of 0.20 mg was administered by IV bolus. The subject was observed for signs or symptoms of withdrawal assessed using the COWS. If no evidence of withdrawal occurred within 30 seconds, an additional 0.6 mg of naloxone was administered by IV bolus. The subject was observed for 5 minutes for signs and symptoms of withdrawal through an additional assessment of the COWS. Total scores for the scale range from 0 to 48 with scores of 5-12 indicating mild withdrawal; scores of 13-24 indicating moderate withdrawal; scores of 25-36 indicating moderately severe withdrawal; and scores > 36 indicating severe withdrawal. Subjects successfully passed the Naloxone Challenge Test if they had a COWS score of < 5 following challenge with naloxone, which indicates the absence of withdrawal signs.

Qualification Phase (Drug Discrimination Test)

Subjects who pass the Naloxone Challenge Test will then participate in the Qualification Phase (called the Drug Discrimination Test by the Sponsor), which ensures that subjects can tolerate and differentiate between the effects of a single intravenous dose of 0.5 mg/kg pentazocine and placebo. At least 12 hours will separate the Naloxone Challenge Test and Qualification Phase. This is acceptable, given that naloxone has a half-life that is less than 90 minutes. A training session will be provided for the subjective measures prior to drug administration in the Qualification Phase.

Subjects received either pentazocine (0.5 mg/kg, i.v.) or placebo (i.v.) on Day 1 and Day 2 (e.g., a 24 hour washout) in a two-way crossover, double-blind, randomized design. Given that the half-life of pentazocine is ~2-3 hours, a 24 hour washout period is adequate. Pentazocine was selected as the positive control because it is a kappa opioid agonist and mu opioid partial agonist. The 0.5 mg/kg dose was selected on the basis of its use in previous HAP studies.

The only endpoint used to determine eligibility for proceeding in the study will be VAS Drug Liking on a bipolar 0-100 point scale. However, secondary subjective measures and vital signs

used in the Treatment Phase will also be collected (see below), to familiarize the subject with the measures prior to their use in the Treatment Phase.

In order to qualify for the Treatment Phase, subjects must have a response on VAS Drug Liking that shows:

1) a minimum score of 70 out of 100 points in response to pentazocine
2) at least a 15-point difference between pentazocine and placebo treatments during the first 2 hours following drug administration, and
3) a placebo response between 40-60 points (inclusive) during the first 2 hours following drug administration.

Treatment Phase

Subjects who successfully completed both parts of the Qualification Phase were eligible to enter the Treatment Phase. Subjects received the following intravenous treatments in a randomized, double-blind crossover manner based on a 4 x 4 Williams Square randomization scheme, separated by a 48-hour washout period:

- Difelikefalin - 5 μg/kg (10X proposed therapeutic dose)
- Difelikefalin - 15 μg/kg (30X proposed therapeutic dose)
- Pentazocine - 0.5 mg/kg
- Placebo

Given that the half-life of both difelikefalin and pentazocine is ~2 hours, a 48 hour washout period is adequate.

Drug administration occurred at 8 a.m. Each treatment was administered as a 1.0 ml intravenous injection over 30 seconds. Subjects fasted 8 hours prior to dosing and 2 hours postdose. This timing suggests that breakfast was served in the middle of subjective measurement collection, between 2-3 hours after drug administration.

The primary endpoint was VAS Emax for Drug Liking on a bipolar 0-100 point scale.

The secondary endpoints included the following measures, all of which are on a 1-100 point scale, and are unipolar unless designated as bipolar:

- Any Drug Effects VAS
- Good Drug Effects VAS
- High VAS
- Bad Drug Effects VAS
- Feeling Sick VAS
- Nausea VAS
- Sleepiness VAS
- Dizziness VAS
- Spaced Out VAS

- Floating VAS
- Detachment VAS,
- Hallucinations VAS
- Alertness/Drowsiness VAS
- Overall Drug Liking VAS (bipolar)
- Take Drug Again VAS (bipolar)
- Drug Similarity VAS
- Price Value Assessment Questionnaire (PVAQ)
- Hallucinogen Rating Scale (HRS)

VAS for Drug Liking was collected postdose at 5 minutes and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, and 8 hours. VAS scores for High, Sick, Nausea, Sleepy, Dizzy, Spaced Out, Floating, Detached, and Hallucinations were collected predose and at 5 minutes and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, and 8 hours postdose. Alert/Drowsy was collected predose and at 0.5, 1, 2, 4, and 8 hours postdose. HRS was collected at 4 hours postdose. Drug Similarity, Overall Drug Liking, Take Drug Again, and PVAQ were collected at 8 hours postdose.

Pupillometry was also collected predose and at 0.5, 0.75, 1, 1.5, 2, 3, 4, and 8 hours postdose.

Safety assessments included monitoring of AEs, physical examination, supine 12-lead ECG, fluid balance and serum sodium monitoring and clinical laboratory tests (hematology, serum chemistry, serology, and urinalysis). Vital signs were also monitored, including blood pressure, pulse rate, oxygen saturation, and respiratory rate were monitored. Blood samples were collected at predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, and 8 hours postdose in order to determine pharmacokinetic parameters.

Subjects were encouraged to drink fluids throughout their stay in the study unit. Beginning on Day 3 of the Qualification Phase (i.e., beginning of the washout period, at approximately 8:00 a.m.), fluid balance was monitored throughout the in-clinic stay at pre-specified intervals. Subjects received oral rehydration or, if necessary, IV dextrose 5% in water in order to maintain a close to neutral fluid balance.

Results

The Sponsor conducted an analysis of the data using data from all completers (n = 39). They also conducted an analysis with a "Modified Completer Set" that evaluated only 37 subjects, after two subjects were excluded "due to a Drug Liking E_{max} for placebo greater than 60 out of 100 and a difference between Drug Liking E_{max} for placebo and pentazocine that was less than 5 out of 100."

The following analysis of the HAP study subjective measures presented below in quotations is the **verbatim** statement from the Statistical Review and Evaluation of the present HAP study, as conducted by Dr. Wei Liu ("the reviewer"), FDA Office of Biostatistics, April 14, 2021.

"The Agency recommended in the Meeting Minutes to the 5/13/2020 pre-NDA meeting that the primary analysis should be carried out following the 2017 FDA guidance *Assessment of Abuse Potential of Drugs*, using Completer population.

"The Sponsor's statistical analysis of difelikefalin's abuse potential were primarily carried out on the Modified Intention-to-Treat (MITT) population, which is not recommended in the 2017 FDA guidance *Assessment of Abuse Potential of Drugs*, thus are not considered as appropriate.

"The reviewer's primary analysis was conducted on Completers population. This reviewer confirmed the following findings:

> (1) The validation test for comparing the mean Drug Liking VAS Emax between pentazocine 0.5 mg/kg and placebo was statistically significant; the lower 95% confidence limit (one-sided) of the mean difference was 31.4 points, greater than the test margin of 15 points.
>
> (2) For the primary outcome of Drug Liking VAS, the mean Emax of pentazocine 0.5 mg/kg was statistically significantly greater than that of each dose of [difelikefalin], suggesting that that [difelikefalin] (0.005 and 0.015 mg/kg) was less liked than pentazocine 0.5 mg/kg in healthy, recreational polydrug users with lifetime and recent hallucinogenic users;
>
> (3) There was no sufficient evidence to reject the null hypothesis of the mean Emax difference between [difelikefalin] (at either dose) and placebo being greater than the margin of 11 points at a level of 0.05 (one-sided), suggesting that [difelikefalin] still has abuse potential.

"The results of the primary analysis were supported by the analysis of secondary endpoints, Emax of High VAS, Good Drug Effects VAS, and Any Drug Effects VAS. Additional supportive results to CR845's abuse potential come from its consistent positive dose response in the mean Emax of Drug Liking VAS, High VAS, Good Drug Effects VAS, Bad Drug Effects VAS, Any Drug Effects VAS, and for pupillary diameter reduction."

Although the FDA statistical analysis concludes that difelikefalin has abuse potential, CSS does not agree with this conclusion. As described below, positive signals of abuse are seen only in a limited number of subjective measures in which the mean scores are barely outside of the acceptable placebo range and are far below the responses garnered from the positive control drug, pentazocine. Additionally, abuse potential is not determined from a single study, and involves the assessment of all of the abuse-related *in vitro*, animal, and human evaluations with difelikefalin.

Table 1 depicts the effects of study treatments on selected abuse-related subjective measures that were collected in this study, based on data that were evaluated by Dr. Liu.

The subjective measures of Drug Liking, Take Drug Again, and Overall Drug Liking are bipolar scales ranging from 0-100 with 50 as neutral, and an acceptable placebo range of 40-60. The measures Good Drug Effects, High, and Bad Drug Effects are unipolar scales ranging from 0-100 with 0 as neutral and an acceptable placebo range of 0-20.

Table 1: Effects of Intravenous Placebo, Pentazocine (0.5 mg/kg), and Difelikefalin (5 and 15 µg/kg) on Subjective Measures (VAS) – E_{max} Scores (scale 0-100, least squared mean and standard error) (n = 39)

	Placebo	Pentazocine 0.5 mg/kg	Difelikefalin 5 µg/kg	Difelikefalin 15 µg/kg
Drug Liking (bipolar)	53 ± 1	88 ± 2 *	66 ± 2 ^	67 ± 2 ^
Overall Drug Liking (bipolar)	51 ± 1	73 ± 4	52 ± 3 ^	50 ± 3 ^
Good Drug Effects (unipolar)	1 ± 0	12 ± 3 *	39 ± 2 ^	41 ± 2 ^
High (unipolar)	4 ± 2	83 ± 3 *	40 ± 5 ^	41 ± 5 ^
Take Drug Again (bipolar)	49 ± 1	69 ± 4	49 ± 4 ^	45 ± 4 ^
Bad Drug Effects (unipolar)	1 ± 1	9 ± 3 *	2 ± 1	5 ± 2
Any Drug Effects (unipolar)	5 ± 2	86 ± 3 *	45 ± 5 ^	46 ± 5 ^

* = $p < 0.0001$ compared to placebo, ^ = $p < 0.0001$ compared to pentazocine

Study Validation

As shown in Table 1, the positive control drug, pentazocine (0.5 mg/kg), produced the expected increase in positive subjective response on the primary measure of Drug Liking (88 out of 100, respectively), which is outside the acceptable placebo range (40-60 out of 100 on a bipolar scale) and was statistically significantly greater than those produced by placebo. This validates the study.

Drug Liking and Overall Drug Liking

- On the Drug Liking primary measure, difelikefalin at 5 and 15 µg/kg produced an increase in response (66 and 67 out of 100, respectively) on a bipolar scale that was just outside of the acceptable placebo range (40-60 out of 100). Placebo produced a score of 53 that was within the acceptable placebo range. In contrast, pentazocine produced a score of 88 out of 100. Peak subjective responses for both difelikefalin and pentazocine both occurred at ~5 minutes after intravenous administration of the drugs.

- On the Overall Drug Liking measure, difelikefalin at 5 and 15 µg/kg produced scores (52 and 50, respectively) that were similar to placebo (51 out of 100), each of which were

within the acceptable placebo range (40-60 out of 100). In contrast, pentazocine produced a score of 73 out of 100.

Good Drug Effects, High, Take Drug Again, and Bad Drug Effects

- For Good Drug Effects, difelikefalin at 5 and 15 μg/kg produced a response (39 and 41 out of 100) on a unipolar scale that was outside of the acceptable placebo range (0-20 out of 100 on a unipolar scale). However, these scores are numerically half of that produced by pentazocine (82 out of 100). Placebo produced a score of 5 out of 100.

- For High, difelikefalin at 5 and 15 μg/kg produced a response (40 and 41 out of 100) on a unipolar scale that was outside of the acceptable placebo range (0-20 out of 100 on a unipolar scale). However, these scores are numerically half of that produced by pentazocine (83 out of 100). Placebo produced a score of 4 out of 100.

- For Take Drug Again, difelikefalin at 5 and 15 μg/kg produced a response (49 and 46 out of 100) that was within the acceptable placebo range for a bipolar scale (40-60 out of 100) and similar to that produced by placebo (49 out of 100). Pentazocine produced a score (69 out of 100) that was just outside of the acceptable placebo range.

- For Bad Drug Effects, difelikefalin at 5 and 15 μg/kg produced an increase in response (12 and 18 out of 100, respectively) that was within the acceptable placebo range (0-20 for unipolar scales). Placebo and pentazocine also produced scores that were within the acceptable placebo range (1 and 19 out of 100, respectively).

The FDA statistician did not calculate mean and standard deviation for the other VAS measures. However, the Sponsor provided the following summary of the results from these secondary measures, as shown in Table 2. The subjective measures (VAS for Feeling Sick, Nausea, Sleepiness, Dizziness, Spaced Out, Floating, Detachment, and Hallucinations) in the table are unipolar scales ranging from 0-100 with 0 as neutral and an acceptable placebo range of 0-20. The scores for Alertness/Drowsiness were calculated by the Sponsor by subtracting each subject's lowest score on the measure from their baseline predose measurement, and thus represents a change score, not an absolute score on the bipolar scale.

Table 2: Effects of Intravenous Placebo, Pentazocine (0.5 mg/kg), and Difelikefalin (5 and 15 µg/kg) on Secondary Subjective Measures (VAS) – E_{max} Scores (scale 0-100, mean and standard deviation) (n = 40-41)

	Placebo	Pentazocine 0.5 mg/kg	Difelikefalin 5 µg/kg	Difelikefalin 15 µg/kg
Feeling Sick (unipolar)	1 ± 2	12 ± 21	7 ± 13	6 ± 13
Nausea (unipolar)	1 ± 3	14 ± 22	6 ± 12	6 ± 12
Sleepiness (unipolar)	2 ± 8	30 ± 35	12 ± 21	14 ± 22
Dizziness (unipolar)	1 ± 3	23 ± 24	8 ± 13	8 ± 12
Spaced Out (unipolar)	4 ± 11	39 ± 31	16 ± 23	18 ± 23
Floating (unipolar)	1 ± 4	39 ± 37	14 ± 22	13 ± 20
Detachment (unipolar)	1 ± 1	24 ± 31	8 ± 14	10 ± 17
Hallucinations (unipolar)	1 ± 4	6 ± 12	1 ± 2	3 ± 12
Alertness/Drowsiness (change score)	1 ± 6	9 ± 15	2 ± 6	5 ± 11

Since the statistics were not conducted by the FDA statistician, they are only described based on means. Difelikefalin at either 5 µg/kg and 15 µg/kg did not produce scores on any of the VAS measures in Table 2 that were outside of the acceptable placebo range (0-20). Similarly, placebo produced scores on these measures that were within the acceptable placebo range. In contrast, pentazocine produced scores that were far outside the acceptable placebo range for the following VAS measures: Sleepiness (30), Spaced Out (39), and Floating (39). On the remaining VAS measures, pentazocine produced scores that were within the acceptable placebo range or just slightly outside of it. Thus, difelikefalin did not produce any signals of abuse potential on these secondary subjective measures.

Drug Similarity

For the Drug Similarity VAS measure, subjects did not rate difelikefalin at either 5 µg/kg and 15 µg/kg as similar to benzodiazepines, cannabinoids, hallucinogens, opioids, or stimulants (scores <25 out of 100 on each VAS measure). Subjects also did not rate placebo as similar to any of these drug classes. In contrast, pentazocine was rated as similar to opioids (score of 60 out of 100), but dissimilar to the other drug classes. These data show that difelikefalin does not produce effects that are similar to known drugs of abuse, including opioids.

Hallucinogen Rating Scale

Difelikefalin (5 μg/kg and 15 μg/kg) and pentazocine produced scores on all 6 subscales of the Hallucinogen Rating Scale (Affect, Cognition, Intensity, Perception, Somaesthesia, Volition) that were similar to those produced by placebo. Thus, difelikefalin does not produce hallucinogenic responses.

Price Value Assessment

On the Price Value Assessment, pentazocine produced a relatively high monetary value ($9.60). In contrast, the monetary value assigned for the other three treatments was much lower: placebo ($1.10), difelikefalin 5 μg/kg ($2.60) and difelikefalin 15 μg/kg ($3.90). These data suggest that difelikefalin does not produce rewarding properties that would lead to a high level of value as a street drug.

Pupillometry

Reductions in pupil size were negligible for placebo (0.6 mm), and for both doses of difelikefalin (0.4 mm for each dose). In contrast, pentazocine produced a large reduction in pupil size (2.5 mm). These data demonstrate that difelikefalin does not produce the miosis associated with opioids.

Adverse Events

As shown in Table 3, there were no reports of euphoria or hallucinations following intravenous administration of difelikefalin at either dose (5 μg/kg and 15 μg/kg). Notably, there were also no other CNS-related AEs that indicate abuse potential reported after either dose of difelikefalin. Since the doses of difelikefalin are extremely high for a HAP study (10X and 30X, when we recommended that 1X and 3X doses be tested), and were given via a very fast route of administration, this lack of abuse-related AEs strongly supports the conclusion that difelikefalin does not produce signals of abuse potential.

The AEs that were reported following difelikefalin administration (compared to placebo) are common with many drugs that are CNS active, including dizziness (2.4-12.5% vs. 0%), headache (7.3-10% vs. 2.4%), nausea (2.4-2.5% vs. 0%), and vomiting (0-5% vs. 2.5%). Thus, these AEs also do not provide an abuse-related signal associated with difelikefalin.

Table 3: Summary of Adverse Events Reported by Two or More Subjects in Any Treatment in the Treatment Phase (Safety Population; N (%))

	Placebo	Pentazocine 0.5 mg/kg	Difelikefalin 5 µg/kg	Difelikefalin 15 µg/kg
Nervous System Disorders				
Dizziness	0 (0.0)	2 (5.0)	1 (2.4)	5 (12.5)
Headache	1 (2.4)	4 (10.0)	3 (7.3)	4 (10.0)
Hypoaesthesia	0 (0.0)	1 (2.5)	2 (4.9)	1 (2.5)
Gastrointestinal Disorders				
Abdominal pain (upper)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.0)
Constipation	0 (0.0)	1 (2.5)	0 (0.0)	2 (5.0)
Vomiting	1 (2.4)	5 (12.5)	0 (0.0)	2 (5.0)
Dyspepsia	0 (0.0)	0 (0.0)	2 (4.9)	1 (2.5)
Nausea	0 (0.0)	5 (12.5)	1 (2.4)	1 (2.5)
Administration Site Conditions				
Chills	0 (0.0)	2 (5.0)	1 (2.4)	0 (0.0)
Tissue Disorders				
Groin pain	0 (0.0)	0 (0.0)	2 (4.9)	1 (2.5)
Vascular Disorders				
Hot flush	0 (0.0)	3 (7.5)	0 (0.0)	0 (0.0)

Safety: Vital Signs

There were no clinically meaningful changes from baseline in vital signs (blood pressure, pulse rate, oxygen saturation, and respiratory rate) following administration of difelikefalin at the two doses administered.

Overall Conclusions

In a human abuse potential study with subjects experienced with opioids and psychedelics, difelikefalin did not produce meaningful signals of abuse potential on positive subjective measures such as VAS for Drug Liking, Overall Drug Liking, Good Drug Effects, High, or Take Drug Again. On the VAS for Drug Similarity, difelikefalin did not produce scores of similarity for major classes of drugs of abuse, including benzodiazepines, cannabinoids, hallucinogens, opioids, or stimulants. Difelikefalin did not produce increases on the Hallucinogen Rating Scale, demonstrating it does not produce psychedelic effects. On the Price Value Assessment, difelikefalin was rated as having a low monetary value. There were no changes in pupil size compared to placebo. None of the adverse events produced by difelikefalin included euphoria or hallucinations. These data suggest that difelikefalin does not appear to have abuse potential.

4.2 Abuse-Related Adverse Events in Clinical Studies

a. Phase 1 Studies (CR845-100201, CR845-CLIN1001, CR845-CLIN1009, PR-13A9-P1-A, CR845CLIN1004, and PR-13A9-P1-A.

To identify potential safety signals following intravenous administration of difelikefalin in healthy individuals, abuse-related adverse events from 6 Phase 1 studies were evaluated. These included 4 single-dose studies (n = 145) and 2 multiple-dose studies (n = 58).

As shown in Tables 4 and 5, during the 6 Phase 1 studies with healthy individuals, there were no reports of euphoria during single dose studies (0 of 145 subjects, 0%) and there was only one report of euphoria during multiple-dose studies (1 of 58 subjects, 1.7%). Euphoria was reported in 1 of 97 subjects who received placebo (1.0%) but in none of the subjects who received placebo on multiple occasions. Similarly, there was only 1 report of hallucination during single-dose studies (1 of 145 subjects, 0.7%) and no reports of hallucination during multiple-dose studies (0 of 58 subjects, 0%). Placebo administration did not lead to any reports of hallucination during single- or multiple-doses studies (0 of 97 subjects (0%) and 0 of 24 subjects (0%), respectively).

Table 4: Number (%) of Healthy Subjects with Abuse-related Adverse Events from Single-dose, Double-blind Studies (All Phase 1 Studies Pooled)

Type of Event Preferred Term	Placebo (N=97)	Difelikefalin				
		0.5 µg/kg (N=54)	>0.5 to ≤5 µg/kg (N=93)	>5 to ≤10 µg/kg (N=20)	>10 µg/kg (N=28)	Overall Difelikefalin (N=145)
Euphoria-related Adverse Events						
Euphoric mood	1 (1.0%)	0	0	0	0	0
Feeling of relaxation	0	0	1 (1.1%)	0	2 (7.1%)	3 (2.1%)
Feeling abnormal	0	0	1 (1.1%)	0	0	1 (0.7%)
Terms Indicative of Impaired Attention, Cognition, and Mood						
Fatigue	1 (1.0%)	0	1 (1.1%)	1 (5.0%)	10 (35.7%)	12 (8.3%)
Somnolence	2 (2.1%)	0	4 (4.3%)	1 (5.0%)	2 (7.1%)	7 (4.8%)
Asthenia	0	0	0	1 (5.0%)	0	1 (0.7%)
Lethargy	0	0	1 (1.1%)	0	0	1 (0.7%)
Dissociative/Psychotic Terms						
Paraesthesia	3 (3.1%)	10 (18.5%)	18 (19.4%)	11 (55.0%)	2 (7.1%)	37 (25.5%)
Hypoaesthesia	0	3 (5.6%)	14 (15.1%)	6 (30.0%)	9 (32.1%)	30 (20.7%)
Hallucination	0	0	0	1 (5.0%)	0	1 (0.7%)

Source: Module 5.3.5.3.2 ISS Post-text Table 4.5.1.1
Studies CR845-100201, CR845-CLIN1001, CR845-CLIN1009, and PR-13A9-P1-A.
Note: Subjects who received both placebo and difelikefalin or more than 1 dosing category of difelikefalin are counted in more than 1 column.

Table 5: Number (%) of Healthy Subjects with Abuse-related Adverse Events from Multiple-Dose, Double-Blind Studies (All Phase 1 Studies Pooled)

Type of Event Preferred Term	Placebo (N=24)	Difelikefalin (Total Daily Dose)		
		>5 to ≤10 µg/kg (N=6)	>10 µg/kg (N=52)	Overall Difelikefalin (N=58)
Euphoria-related Adverse Events				
Euphoric mood	0	0	1 (1.9%)	1 (1.7%)
Feeling abnormal	0	1 (16.7%)	2 (3.8%)	3 (5.2%)
Terms Indicative of Impaired Attention, Cognition, and Mood				
Sedation	0	0	16 (30.8%)	16 (27.6%)
Somnolence	0	0	5 (9.6%)	5 (8.6%)
Fatigue	0	0	3 (5.8%)	3 (5.2%)
Asthenia	0	0	1 (1.9%)	1 (1.7%)
Mood altered	0	0	1 (1.9%)	1 (1.7%)
Dissociative/Psychotic Terms				
Paraesthesia	0	0	22 (42.3%)	22 (37.9%)
Hypoaesthesia	0	0	5 (9.6%)	5 (8.6%)
Amnesia	0	0	2 (3.8%)	2 (3.4%)
Disorientation	0	0	2 (3.8%)	2 (3.4%)
Anxiety	0	0	1 (1.9%)	1 (1.7%)
Confusional state	0	0	1 (1.9%)	1 (1.7%)
Irritability	0	0	1 (1.9%)	1 (1.7%)

Source: Module 5.3.5.3.2 ISS Post-text Table 4.5.1.3
Studies included: CR845CLIN1004 and PR-13A9-P1-A.
Note: Subjects who received both placebo and difelikefalin or more than 1 dosing category of difelikefalin are counted in more than 1 column.

In the absence of meaningful signals for euphoria or hallucinations, other CNS-related AEs are not considered to be abuse-related. The CNS-related AEs that were reported in single-dose studies at a rate of >2% (compared to placebo) include: paresthesia (25.5% vs. 3.1%), and hypoaesethesia (20.7% vs. 0%), fatigue (8.3% vs 1.0%), somnolence (4.8% vs. 2.1%), and feeling of relaxation (2.1% vs. 0%). In multiple-dose studies, the CNS-related AEs that were reported at a rate of >2% (compared to placebo) include: sedation (27.6% vs. 0%), somnolence (8.6% vs. 0%), feeling abnormal (5.2% vs. 0%), and fatigue (5.2% vs. 0%).

b. Phase 2/3 Studies (CR845-CLIN1003. CLIN3101, CR845-CLIN3102 OLE, CR845-CLIN3103 OLE, and CR845-CLIN3105)

To identify potential safety signals following intravenous administration of difelikefalin in healthy individuals, abuse-related adverse events from 5 Phase 2/3 studies were evaluated. These included 1 single-dose study (n = 18) and 4 multiple-dose studies (n = 1257).

As shown in Tables 6 and 7, during the 5 Phase 2/3 studies with healthy individuals, there were no reports of euphoria or hallucinations during single dose studies (0 of 18 subjects, 0%) or multiple-dose studies (0 of 1257 subjects, 0%).

Table 6: Number (%) of Subjects with Abuse-related Adverse Events in Single-dose, Double-Blind Studies of Subjects with Chronic Kidney Disease Undergoing Hemodialysis (All Studies Pooled)

Type of Event Preferred Term	Placebo (N=6)	Difelikefalin		
		>0.5 to ≤5 µg/kg (N=12)	>5 to ≤10 µg/kg (N=6)	Overall Difelikefalin (N=18)
Euphoria-related Adverse Events				
Feeling drunk	0	0	1 (16.7%)	1 (5.6%)
Feeling of relaxation	0	0	1 (16.7%)	1 (5.6%)
Terms Indicative of Impaired Attention, Cognition, and Mood				
Somnolence	1 (16.7%)	2 (16.7%)	0	2 (11.1%)
Asthenia	0	0	1 (16.7%)	1 (5.6%)
Fatigue	0	1 (8.3%)	0	1 (5.6%)
Dissociative/Psychotic Terms				
Paraesthesia	0	3 (25.0%)	1 (16.7%)	4 (22.2%)
Irritability	0	0	1 (16.7%)	1 (5.6%)

Source: Module 5.3.5.3.2 ISS Post-text Table 4.5.1.4
Studies included: CR845-CLIN1003.

Table 7: Number (%) of Subjects with Abuse-related Adverse Events in Multiple-dose, Open-label Studies of Subjects with Chronic Kidney Disease Undergoing Hemodialysis (All Studies Pooled)

Type of Event **Preferred Term**	**Difelikefalin** **0.5 µg/kg** **(N=1257)**
Terms Indicative of Impaired Attention, Cognition, and Mood	
Asthenia	47 (3.7%)
Fatigue	18 (1.4%)
Somnolence	11 (0.9%)
Depression	11 (0.9%)
Dissociative/Psychotic Terms	
Paraesthesia	12 (1.0%)
Hypoaesthesia	10 (0.8%)
Confusional state	8 (0.6%)
Related Terms Not Captured Elsewhere	
Anxiety	25 (2.0%)

Source: Module 5.3.5.3.2 ISS Post-text Table 4.5.1.8
Studies included: CLIN3101, CR845-CLIN3102 OLE, CR845-CLIN3103 OLE, and CR845-CLIN3105

In the absence of meaningful signals for euphoria or hallucinations, other CNS-related AEs are not considered to be abuse-related. The CNS-related AEs that were reported in single-dose studies (n = 18) at a rate of >2% include: paraesthesia (22.2%), feeling drunk (5.6%), feeling relaxation (5.6%), and fatigue (5.6%). In multiple-dose studies (n = 1257), the CNS-related AEs that were reported at a rate of >2% include asthenia (3.7%) and anxiety (2.0%).

Conclusions

Difelikefalin did not produce euphoria or hallucinations in single-dose or multiple-dose trials conducted in Phase 1 studies (healthy individuals) or Phase 2/3 studies (with uremic pruritis patients). This shows that difelikefalin does not produce adverse event evidence of abuse potential.

Difelikefalin produced other CNS-related AEs, but they are not indicative of abuse because of the absence of a meaningful rate of reports of euphoria or hallucination. However, they do strongly demonstrate that difelikefalin penetrates the blood-brain barrier. Thus, it cannot be concluded that difelikefalin is a peripherally-acting drug without clinically-relevant effects on the CNS.

4.3 Assessment of Human Physical Dependence (Study #CR845-100303 and CR845-CLIN3102)

a. Evaluation of Physical Dependence Following 3-Week Difelikefalin Administration

A dedicated human physical dependence evaluation was conducted at 5 study centers with 30 patients undergoing hemodialysis to determine if chronic administration of difelikefalin produces withdrawal signs and symptoms upon drug discontinuation.

Open-Label Drug Administration Phase

Subjects received open-label difelikefalin (0.5 μg/kg, i.v. bolus) at the conclusion of each of 3 dialysis sessions per week, for 3 consecutive weeks. During the 3-week drug administration period, subjects vital signs (oxygen saturation, respiratory rate, body temperature, heart rate, and blood pressure), AEs and clinical laboratory tests were monitored. Baseline assessment of the following instruments were also collected during the drug administration period: Clinical Opiate Withdrawal Scale (COWS), Subjective Opiate Withdrawal Scale (SOWS), visual analog scales (VAS), and Leeds Sleep Evaluation Questionnaire (LSEQ).

Double-Blind Drug Discontinuation or Continued Administration Phase

Following the conclusion of the 3-week drug administration phase, subjects were randomized to either continue receiving difelikefalin or to begin receiving placebo at the conclusion of each of 3 dialysis sessions per week, for 2 consecutive weeks. During the 2-week drug discontinuation (or continued administration) period, subjects vital signs, AEs and clinical laboratory tests were monitored. Assessment of withdrawal signs and symptoms were monitored using the following instruments: Clinical Opiate Withdrawal Scale (COWS), Subjective Opiate Withdrawal Scale (SOWS), visual analog scales (VAS), and Leeds Sleep Evaluation Questionnaire (LSEQ). Responses on VAS for Pain, Feeling Sick, Bad Effects, and Hallucinating were also collected. Intensity of itch was measured using the Worst Itch Numeric Rating Scale (WI-NRS).

Statistical Analysis

The following analysis of the human physical dependence study subjective measures presented below in quotations is the **verbatim** statement from the Statistical Review and Evaluation of the study, as conducted by Dr. Anna Sun ("the reviewer"), FDA Office of Biostatistics, July 7, 2021:

"The reviewer's statistical analysis results

1. In the primary endpoint analysis using the Per-protocol Population, for determination of noninferiority (i.e., withdrawal scores in subjects switched to placebo were not clinically worse than withdrawal scores in subjects continuing to receive difelikefalin), the null hypothesis was defined as a median or mean

difference between placebo and difelikefalin in maximum COWS total score of ≥ 4 points. The analysis results showed that:

- The Hodges-Lehmann estimate of the median difference in maximum COWS total score was 1.00 (CI: -Infty, 2.00), with an upper limit of the CI being less than 4.
- The LS mean difference between placebo and difelikefalin was 0.49 (CI: -Infty, 1.32), the mean difference was not statistically significant (P-value <0.0001).

The results support the noninferiority of withdrawal symptoms for subjects switched to placebo versus subjects continued on difelikefalin.

2. In the sensitivity analysis of the primary endpoint analysis using Full Analysis Population, noninferiority for placebo was also demonstrated: The Hodges-Lehmann estimate of the median difference in maximum COWS total score was 1.00 (CI: -Infty, 2.00), with an upper limit of the CI being less than 4. The mean difference between placebo and difelikefalin was not statistically significant (P-value <0.0001).

3. The secondary endpoint of the treatment difference in COWS total scores at Week 4 and Week 5 also showed noninferiority for clinical withdrawal signs and symptoms in subjects switched from difelikefalin to placebo compared with subjects continuing to receive difelikefalin. The LS mean treatment group differences in COWS total score at Week 4 and Week 5 were 0.66 (CI: -Infty, 1.47) and 0.37 (CI: -Infty, 1.15), respectively. The differences between placebo and difelikefalin for both week 4 and week 5 were not statistically significant (P-values <0.0001).

4. For the secondary endpoint of the treatment difference in maximum SOWS total scores, the results showed that:
    - The Hodges-Lehmann estimate of the median difference in maximum SOWS total score for the Per-protocol Population was 1.00 (CI: -Infty, 4.00), with an upper limit of the CI equals 4.
    - The LS mean values for maximum SOWS Total scores during the Double-blind Phase between the difelikefalin and placebo groups were: 3.24 and 4.05, respectively, with a LS mean difference of 0.81 (CI: -Infty, 2.63). NOTE: The margin used to test noninferiority with respect to maximum SOWS total score is not specified.
5. For the SOWS total scores at Week 4 and Week 5, the LS mean score was higher in the placebo group than in the difelikefalin group: 2.59 versus 1.52 at Week 4, with an LS mean difference of 1.07 (CI: -Infty, 2.10); and 2.38 versus 1.05 at Week 5, with an LS mean difference of 1.33 (CI: -Infty, 2.26).

“Statistical Issues and Concerns:

1. The baseline value that the sponsor used was the average of the non-missing values during the Baseline Period (Day -7 to Day -1).

The baseline value that the reviewer used for primary analysis, sensitivity analysis and secondary analysis was the Mean COWS Derived Total Score in Week 3. The way to measure withdrawal is to measure the symptoms of withdrawal relative to the baseline right before the discontinuation occurs which is derived from week 3 in this case.

2. Since the sample size of this study is small, comparing the median difference between Placebo and CR845 instead of mean difference may be more appropriate.

3. The study days that the sponsor used are shifted by one day from what table 3 (Study Schedule of Assessments) shows. For example, table 3 shows week 4 includes day 22, 24 and 26, while the sponsor used days 24, 26, and 29 for their analysis. This also applies to week 5. Furthermore, the double- blind treatment phase includes **7** days (days 22, 24, 26, 29, 31, 33 and 36) instead of 6 days. Since this is a physical dependence study, the withdraw syndrome may delay and last for a few days. The sponsor should explain why they used these days.

4. The sponsor's secondary analysis includes maximum SOWS total score during the Double-blind Phase. However, the margin used to test noninferiority with respect to maximum SOWS total score is not specified.

5. Is two weeks of treatment phase enough?
The following table shows the number of subjects having the max COWS total score on each day. 18 out of 28 subjects had the max COWS total score at the last 3 visits. Especially for day 36, 11 out of 28 subjects had the max COWS total score on this day. It indicates that subjects had larger responses towards the end of the study. The reviewer is concerned if two weeks of treatment phase is enough to assess the potential of physical withdrawal from intravenous CR845 (difelikefalin) in hemodialysis patients.

Visit Day	Frequency
22	5
24	1
26	3
29	1
31	4
33	3
36	11

"In conclusion, the reviewer's statistical analysis results support the sponsor's conclusion, that in subjects undergoing hemodialysis and treated with difelikefalin for 3 weeks, switching to placebo for 2 weeks did not elicit clinical signs or symptoms of

withdrawal, as measured by maximum COWS total score, relative to subjects who continued treatment with difelikefalin. However, we have noted some specific concerns listed above, we defer to Control Substance Staff (CSS) reviewers' decision."

Conclusions

CSS agrees with the conclusion by Dr. Sun that the data in the dedicated human physical dependence study do not demonstrate that chronic administration of difelikefalin produces withdrawal signs or symptoms indicative of physical dependence.

b. Evaluation of Physical Dependence Following 12-Week Difelikefalin Administration

A human physical dependence evaluation was conducted with CKD-aP patients undergoing hemodialysis to determine if chronic administration of difelikefalin in a Phase 3 study produces withdrawal signs and symptoms upon drug discontinuation.

Drug Administration Phase

Subjects (n = 355) received an intravenous bolus of difelikefalin (0.5 μg/kg) or saline at the conclusion of each of 3 dialysis sessions per week, for 12 consecutive weeks, as part of a Phase 3 study. Standard study procedures and safety measures were followed during this phase. During the study, 55 subjects dropped out of the study and did not enter the Drug Discontinuation Phase.

Drug Discontinuation Phase

At the end of the 12-week drug administration phase, subjects (n = 300) began receiving placebo at the conclusion of each of 3 dialysis sessions per week, for 2 consecutive weeks. During this period, subjects were monitored using the Short Opiate Withdrawal Scale (ShOWS), Objective Opiate Withdrawal Scale (OOWS), body temperature, vital signs, and a structured safety evaluation. The first evaluation using these measures occurred on the first day of drug discontinuation, as a baseline assessment.

The following discontinuation-emergent adverse events are signs and symptoms of withdrawal. They were used as a checklist to evaluate each subject at baseline and throughout the Discontinuation Period:

- Dysphoric mood
- Nausea and/or vomiting
- Muscle aches
- Lacrimation and/or rhinorrhea
- Pupillary dilation, piloerection, and/or sweating
- Diarrhea
- Yawning
- Fever
- Insomnia

- Headache
- Anxiety
- Nausea/vomiting
- Tremor
- Chills
- Decreased concentration
- Agitation/irritability
- Sleep disturbances
- Mood changes

Subject and observer-rated withdrawal scale measures.

On the first day of difelikefalin discontinuation (baseline assessment), there were no differences in ShOWS scores between the difelikefalin and placebo groups (5.5 and 5.9, respectively.

Over the course of the two-week Discontinuation Phase, each of the treatment groups showed a reduction in scores on the ShOWS measure, ending with scores of 4.0 for difelikefalin and 4.4 for placebo on Day 14. A reduction in scores on this measure indicates fewer withdrawal signs and symptoms. If difelikefalin had produced physical dependence, the ShOWS scores would have increased from the baseline assessment of 5.5. The greatest difference in ShOWS scores between the two treatment groups was on Day 4, with 5.3 for difelikefalin (a decrease of 0.2 from baseline) and 4.4 for placebo (a decrease of 1.1 from baseline). However, both of these scores were in the negative direction, indicating a reduction in withdrawal.

The OOWS measure was also used during the Discontinuation Period. At baseline, difelikefalin and placebo groups had similar OOWS scores at baseline (0.2 and 0.3, respectively) and at the end of the Discontinuation Period (0.1 and 0.2, respectively). These scores indicate that there were no observer changes in withdrawal signs and symptoms over the two weeks following difelikefalin discontinuation.

The data from the ShOWS and OOWS show that difelikefalin did not produce classic opioid withdrawal signs and symptoms following drug discontinuation.

Adverse Events and Vital Signs

The adverse event profile during the Discontinuation Period was limited. The AEs that were reported in the difelikefalin group (n = 151) at an incidence of >1.0% (compared to placebo; n = 149) included abdominal pain (n = 3; 2.0% vs. 0%), influenza-type illness (n = 2; 1.3% vs. 0%), headache (n = 2; 1.3% vs. 0%), fall (n = 2; 1.3% vs. 2.7%), and hyperkalemia (n = 2; 1.3% vs. 0.7%). These data show that difelikefalin did not produce classic opioid-withdrawal symptoms following drug discontinuation.

The vital signs of subjects in the difelikefalin and placebo groups were very similar for systolic and diastolic blood pressure, arterial pressure, heart rate, and body temperature between baseline assessments on the first day of difelikefalin discontinuation and the last day of the Discontinuation Period.

Conclusions

Discontinuation of difelikefalin did not produce any signs or symptoms of withdrawal, as evaluated through subjective or objective scales of withdrawal, adverse events, or vital signs, that differed from placebo. Thus, difelikefalin does not appear to produce physical dependence following chronic administration.

5. Regulatory Issues and Assessment

CSS has concluded from the in vitro, animal, and human study data submitted in the NDA for difelikefalin that the drug does not have abuse potential.

Thus, it will not be necessary for CSS to prepare an Eight Factor Analysis that would recommend scheduling of difelikefalin under the Controlled Substances Act.

Similarly, it will (b) (4)

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Signing also for Dr. Chad Reissig

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 8, 2021
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 214916
Product Name and Strength:	Korsuva (difelikefalin) solution for injection, 65 mcg/ 1.3 mL (50 mcg/mL)
Applicant/Sponsor Name:	Cara Therapeutics, Inc.
OSE RCM #:	2020-2730-1
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on June 21, 2021 for Korsuva. Division of Dermatology and Dentistry (DDD) requested that we review the revised container label and carton labeling for Korsuva (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Patel M. Label and Labeling Review for Korsuva (NDA 214916). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 05. RCM No.: 2020-2730.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 28, 2021

To: Gary Chiang, MD, Clinical Reviewer,
Division of Dermatology and Dentistry (DDD)
Amy Woitach, MD, Clinical Team Leader, DDD
Jennifer Harmon, Regulatory Project Manager, DDD

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for KORSUVA® (difelikefalin) injection, for intravenous use

NDA: 214916

In response to DDD's consult request dated January 29, 2021, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for KORSUVA® (difelikefalin) injection, for intravenous use (Korsuva).

Labeling

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DDD on May 20, 2021 and our comments are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on December 23, 2020 and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

OPDP is concerned about the juxtaposition of the proprietary and established names. Per 21 CFR 201.10 (g)(1), proprietary and established names should not be separated by placement of intervening matter that detracts, obfuscates, or de-emphasizes the established name, or obscures the relationship between the proprietary and established names. The stylized design of the bottom right leg of the “K” in the proprietary name is intervening matter as it extends between and separates the proprietary and established name. We recommend revision of the proprietary name. Please apply this comment to all container/closure presentations.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 5, 2021
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	NDA 214916
Product Name, Dosage Form, and Strength:	Korsuva (difelikefalin) solution for injection, [redacted] mL [redacted]/mL) or [redacted] mL (50 mcg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Cara Therapeutics, Inc.
FDA Received Date:	December 23, 2020
OSE RCM #:	2020-2730
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 REASON FOR REVIEW

As part of the approval process for Korsuva (difelikefalin) solution for injection, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Korsuva prescribing information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the Prescribing Information (PI), container label, and carton labeling. We find the PI, container label, and carton labeling can be improved for consistency (consistent unit expression of strength and dose), to facilitation product identification (e.g. replacing National Drug Code placeholder with NDC, adding linear barcode to container label), and to prevent preparation, administration and wrong dose errors [e.g. with complete strength expression - total strength per vial (strength per mL), adding route of administration to carton labeling].

4 CONCLUSION & RECOMMENDATIONS

We reviewed the Prescribing Information (PI), container label, and carton labeling. We find the PI, container label, and carton labeling can be improved for consistency, to facilitation product identification, and to prevent preparation, administration and wrong dose errors. We provide recommendations below in Section 4.1 for the Division and Section 4.2 for the Applicant to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF DERMATOLOGY AND DENTISTRY (DDD)

A. General Comments

1. We note the use of the term [redacted] to describe the product in the Prescribing Information, container label, and carton labeling. We defer to the Office of Pharmaceutical Quality (OPQ) to determine if it is appropriate package type term for this product throughout the labeling. We recommend that the container label and carton labeling be updated to match the correct package type term for consistency.
2. We defer to OPQ on the specific storage information that needs to be included on the carton labeling.

B. Prescribing Information

1. Dosage and Administration Section and Dosage Forms and Strengths section
   a. We note [redacted] The product strength units of measure should match the units of measure described in the DOSAGE AND ADMINISTRATION section of the prescribing information to avoid error. To minimize the incorrect dose errors (e.g. calculation errors, leading zeros), we recommend expressing the total strength and concentration per mL as "mcg per mL". We recommend that the container label and carton labeling be updated to match for consistency.
2. Dosage Forms and Strengths section
   a. To facilitate prescribing and for consistency revise the strength presentation to include the concentration per milliliter (e.g. [redacted] per mL).
3. How Supplied/Storage and Handling Section
   b. We note the use of the placeholders 'XXXXX-XX-XX' for the National Drug Code (NDC) and recommend replacing these NDC placeholders with the actual NDC when it is determined.
   c. As presented, the strength expression is incomplete. Revise the strength expression to include the concentration in parentheses after the total strength per total volume, where it appears in the PI.

4.2 RECOMMENDATIONS FOR CARA THERAPEUTICS, INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. As currently presented the National Drug Code (NDC) is denoted by a placeholder (NDC XXXXX-XXX-X). Replace these NDC placeholders with the actual NDC when it is determined and submit the revised labels and labeling to the Agency for review. Please note, the container label of one vial and the carton

labeling of (b) (4) vials should have different NDC package codes (last 2 digits of the NDC).

2. As currently presented, the total strength per vial for Korsuva is not provided. Omission of the product's total strength may lead to preparation and administration errors. We recommend adding the product strength expressed as total strength per total volume prominently in front of or directly above the concentration per mL[a] .

B. Container Label

1. The drug barcode is often used as an additional verification before drug administration in the hospital setting; therefore, it is an important safety feature that should be part of the label whenever possible. Therefore, we request you add the product's linear barcode to each individual vial as required per 21CFR 201.25(c)(2). Consider reorienting the linear barcode to a vertical position to improve the scannability of the barcode. Barcodes placed in a horizontal position may not scan due to vial curvature.[b]

2. Add the route of administration to the principal display panel (PDP) of the container label, as per Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013.

3. To ensure consistency with the Prescribing Information, revise the statement, (b) (4) if space permits. If space does not permit, remove the (b) (4) statement.

C. Carton Labeling

1. To ensure consistency with the Prescribing Information, revise the statement, (b) (4) to read "Recommended Dosage: See prescribing information."

[a] United States Pharmacopoeia (USP) General Chapter <1> Injections.

[b] Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Korsuva received on December 23, 2020 from Cara Therapeutics, Inc..

Table 2. Relevant Product Information for Korsuva	
Initial Approval Date	N/A
Active Ingredient	difelikefalin
Indication	treatment of moderate-to-severe pruritus associated with chronic kidney disease (CKD-aP) in adult patients undergoing hemodialysis (HD).
Route of Administration	intravenous
Dosage Form	solution for injection
Strength	(b) (4) mL (b) (4) /mL)
Dose and Frequency	0.5 mcg/kg administered by intravenous bolus injection at the end of each HD treatment
How Supplied	sterile, colorless solution in single use, glass vials. Each vial contains (b) (4) mL of KORSUVA solution (b) (4) mL. (b) (4) vials packaged in a box containing 12 vials
Storage	Vials must be stored (b) (4) °C, with excursions to 15° to 30°C (*see* USP Controlled Room Temperature). Patients must be dosed within 60 minutes of syringe preparation; prepared syringes can be stored at ambient temperature until dosing.
Container Closure	glass vials

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Korsuva labels and labeling submitted by Cara Therapeutics, Inc..

- Container label received on December 23, 2020
- Carton labeling received on December 23, 2020
- Prescribing Information (Image not shown) received on December 23, 2020, available from \\CDSESUB1\evsprod\nda214916\0001\m1\us\114-label\1141-draft-label\proposed.pdf

G.2 Label and Labeling Images

Container Label

(b) (4)

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[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 214916
Submission Number	001 (New NDA)
Submission Date	12/23/2020
Date Consult Received	1/6/2021
Drug Name	difelikefalin
Indication	Treatment of moderate-to-severe pruritus associated with chronic kidney disease in adult patients undergoing hemodialysis.
Therapeutic dose	0.5 mcg/kg (IV bolus)
Clinical Division	DDD

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult dated 1/6/2021 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT protocol review dated 07/06/2018 in DARRTs (link);
- Previous IRT protocol review dated 02/14/2019 in DARRTS (link);
- Sponsor's cardiac safety report # CR845-100201 (SN0001; link);
- Sponsor's clinical study report # CR845-100201 (SN0001; link);
- Sponsor's statistical analysis plan # CR845-100201 (SN0001; link);
- Sponsor's proposed product label (SN0001; link); and
- Highlights of clinical pharmacology and cardiac safety (SN0002; link).

1 SUMMARY

No significant QTc prolongation effect of difelikefalin was detected in this QT assessment.

The effect of difelikefalin was evaluated in a thorough QT study (Study # CR845-100201). This was a Phase 1, single-dose, randomized, double-blind, placebo controlled, positive-controlled (open-label), 4 arm crossover study. The highest dose evaluated was 3 µg/kg, which covers the worst-case exposure scenario (severe renal impairment, Section 3.1). The data were analyzed using by-time analysis as the primary analysis, which did not suggest that difelikefalin is associated with significant QTc prolonging effect (refer to Section 4.3) – see Table 1 for overall results.

The study included moxifloxacin as a positive control and assay sensitivity was established using by-time analysis (Section 4.3.1.1) and exposure-response analysis (Section 4.5.1). The findings of this analysis are further supported by the available nonclinical data (Sections 3.1.2), exposure-response analysis (Section 4.5), and categorical analysis (Section 4.4).

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

ECG Parameter	Treatment	Time (hr)	ΔΔQTcF (msec)	90% CI (msec)
QTc	CR845 0.5 mcg/kg	1.0	1.7	(-0.2, 3.5)
QTc	CR845 3 mcg/kg	1.0	1.3	(-0.6, 3.1)

For further details on the FDA analysis, please see Section 4.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN001 (link) from the IRT. Our changes are highlighted (addition, ~~deletion~~). Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

At a dose 6 times the maximum approved recommended dose, (b) (4) does not prolong the QT interval to any clinically relevant extent.

We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Cara Therapeutics, Inc. is developing difelikefalin for the treatment of pruritus associated with chronic kidney disease in hemodialysis patients. Difelikefalin (CR845; MW: 679.4 g/mol) is a synthetic peptide amide kappa-opioid receptor agonist. The sponsor states that

its actions are believed to be mediated through multifactorial (e.g., sleep loss, depression, inflammation, and infection) pathways.

The product is formulated as a solution for injection (single-use glass vial) containing (b) (4) for intravenous administration. The proposed therapeutic dose is 0.5 µg/kg to be administered as an intravenous bolus injection at the end of each hemodialysis session (every 2-3 days). The peak concentrations of 6.5 ng/mL (Tmax: ~0.083 h; half-life: ~23 to 41 h) are expected at steady-state with the anticipated therapeutic dose in hemodialysis patients with moderate-to severe pruritus (Study # CR845-CLIN2101). No significant accumulation is expected at steady-state with the proposed maximum therapeutic dose (3 times a week for 8 weeks; Study # CR845-CLIN2101). The maximum tolerated dose is 6 µg/kg (Study # CR845-CLIN1003; Cmax: 31 ng/mL) and multiple doses higher than 2.5 µg/kg have not been evaluated (Study # CR845-CLIN2005; Cmax: 24.4 ng/mL).

Sponsor claims that difelikefalin has a low drug interaction potential as a victim drug and no formal clinical drug interaction studies have been conducted by the sponsor. Considering a small peptide drug which is predominantly cleared renally (~90%; Study # CR845-CLIN1005), severe renal impairment indicates a worst-case clinical scenario. Half-life ranges between 23 and 31 hours in HD subjects compared with a typical range of 2 to 3 hours in subjects with normal renal function. The sponsor states that considerable fraction (with low protein binding) is cleared during dialysis resulting in a relatively low accumulation (~1.2) at the steady-state. Although mean total exposure (AUCinf) was higher for subjects with moderate (171%) and severe (334%) renal impairment relative to subjects with normal renal function, there was no considerable impact on Cmax (mild: 47 ng/mL; moderate: 33 ng/mL; and severe: 41 ng/mL vs normal: 40 ng/mL; Dose: 3 µg/kg).

Previously, the sponsor proposed to evaluate QT effects of their product in a thorough QT study (Study # CR845-100201). This was a Phase 1, single-dose, randomized, double-blind (except for moxifloxacin), placebo controlled, positive-controlled, single site, 4 arm crossover study evaluating the effects of therapeutic (0.5 µg/kg; bolus) and supratherapeutic (3 µg/kg; bolus) IV doses of difelikefalin on the QTc interval in healthy subjects (58 randomized and 47 completed all 4 treatments). Subjects were randomized to a treatment sequence consisting of 4 treatment periods with a minimum 5-day washout between treatments. PK samples were obtained in all subjects on Day 1 of each treatment period of this trial. The ECG samples were obtained on Day 1 at pre-dose (-0.25 h), and post-dose at 0.083, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 18 and 23 h post-dose. Refer to the previous IRT protocol reviews dated 07/06/2018 and 02/14/2019 in DARRTS.

3.1.2 Nonclinical Safety Pharmacology Assessments

Refer to the non-clinical overview (m2.4) and previous IRT protocol reviews dated 07/06/2018 and 02/14/2019 in DARRTS. The sponsor's data indicate that difelikefalin at concentrations up to 1000 µM did not significantly inhibit hERG channel conductance in vitro (≤7.2% inhibition) (Study # CR845-SP037).

The effect of CR845 on the hERG encoded cardiac potassium channel was studied in HEK293 cells. There was no effect on hERG tail currents at 10 µM and 100 µM. At 1 mM, the highest concentration tested, hERG tail currents were reduced by 7.2%, indicating an IC50 > 1 mM.

In monkeys, administration of CR845 resulted in decreased blood pressure, heart rate, and body temperature, which seemed to correlate with the general state of arousal. There were no effects attributable to CR845 on quantitative (PR, QRS, QT, and heart rate-corrected QT interval [QTc, Bazett's] intervals) or qualitative electrocardiogram (ECG) assessments.

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

By-time is the primary analysis for this review. Difelikefalin (CR845) excluded the 10 msec threshold at the supratherapeutic dose level for ΔΔQTcF.

Sponsor also presented by-time analysis for other intervals.

Reviewer's comment: *FDA reviewer's analysis results are similar to the sponsor's results.*

3.2.1.1 Assay Sensitivity

Assay sensitivity was established by the moxifloxacin arm.

Reviewer's comment: *FDA reviewer's analysis results also show that assay sensitivity was established by the moxifloxacin arm. The results of the sponsor's exposure-response analysis also indicate that the study demonstrated assay sensitivity. Please see Section 4.3.1.1 and 4.5.1 for additional details.*

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., > 500 msec or > 60 msec over baseline, PR (>220 msec and 25% over baseline) and QRS (>120 msec and 25% over baseline). One subject experienced HR greater than 100 beats/min in CR845 0.5 mcg/kg IV group.

Reviewer's comment: *FDA reviewer's categorical analysis results are similar to the sponsor's analysis results.*

3.2.3 Exposure-Response Analysis

As an additional analysis, the sponsor also performed PK/PD analysis to explore the relationship between plasma concentration of difelikefalin and ΔQTcF (change from baseline in QTcF) using a linear mixed-effects approach. The sponsor's model included plasma concentration, time (categorical), treatment (active vs placebo), and a baseline adjustment (baseline value minus the mean placebo baseline value) with random subject effects on plasma concentration and the intercept included in the model.

The sponsor's analysis shows that there was no significant slope (p-value=0.3027) for the relationship between ΔQTcF and concentration of difelikefalin. Based on the linear model the predicted ΔΔQTcF was -1.3 msec (upper 90% CI: -0.8 msec) at the mean Cmax of 4.7 ng/mL at therapeutic dose (0.5 µg/kg) and -0.2 msec (upper 90% CI: 0.9 msec) at the mean Cmax of 27.6 ng/mL at supra-therapeutic dose (3 µg/kg). The sponsor's analysis indicates an absence of significant QTc prolongation upon application of difelikefalin.

Reviewer's comment: The conclusion of the reviewer's analysis agreed with the sponsor's analysis. Please see Section 4.5 for details.

3.2.4 Safety Analysis

No deaths or SAEs occurred during the study.

No TEAEs led to treatment period discontinuations. Of the 58 subjects dosed, 27 (46.6%) reported 77 TEAEs.

The most frequently reported TEAEs (reported by ≥4 subjects) included paresthesia reported in 22% subjects, hypoesthesia in 12% subjects, muscle tightness in 16% subjects, and dysmenorrhea in 7% subjects. All TEAEs were mild in severity. One subject left the study due to an unrelated adverse event (stabbing) that occurred between treatment periods while the subject was away from the study site. One subject left the study due to pregnancy detected at Day 1 screening for Treatment Period 2. The 25-year-old female subject had received CR845 0.5 mcg/kg in Treatment Period 1. Delivery was uneventful and mother and child were reportedly healthy at follow-up.

No clinically important or significant safety findings were observed with respect to laboratory, vital sign, or ECG results.

Reviewer's comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no large increases or decreases in heart rate (i.e. |mean| < 10 beats/min) were observed (see Section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT Bias Assessment

Not Applicable.

4.3 BY TIME ANALYSIS

The analysis population used for by time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer used linear mixed model to analyze the drug effect by time for each biomarker (e.g., ΔQTcF, ΔHR, ΔPR and ΔQRS) independently. The model included treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects and baseline as a covariate. The model also included subject as a random effect and an unstructured covariance matrix to explain the associated between repeated measures within period.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups. The maximum ΔΔQTcF values by treatment are shown in Table 2.

Figure 1: Mean and 90% CI of ΔΔQTcF Timecourse (unadjusted CIs).

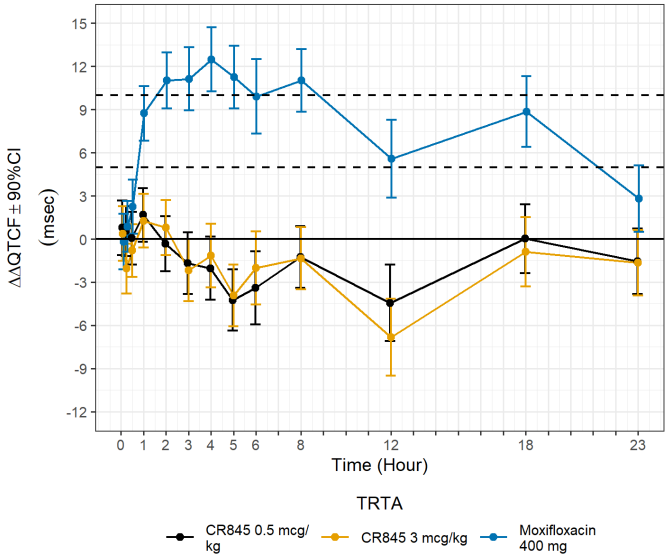


Table 2: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTcF

Actual Treatment	Nact / Npbo	Time (Hour)	ΔΔQTcF (msec)	90.0% CI (msec)
CR845 0.5 mcg/kg	54 / 52	1.0	1.7	(-0.2 to 3.5)
CR845 3 mcg/kg	53 / 52	1.0	1.3	(-0.6 to 3.1)

4.3.1.1 Assay sensitivity

Assay sensitivity was assessed using by-time analysis. The statistical reviewer used the same linear mixed model as treatment arms to analyze the moxifloxacin effect by time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The time-course of changes in ΔΔQTcF is shown in Figure 1 and shows the expected time-profile with a mean effect of > 5 msec after Bonferroni adjustment for 4 time points (Table 3).

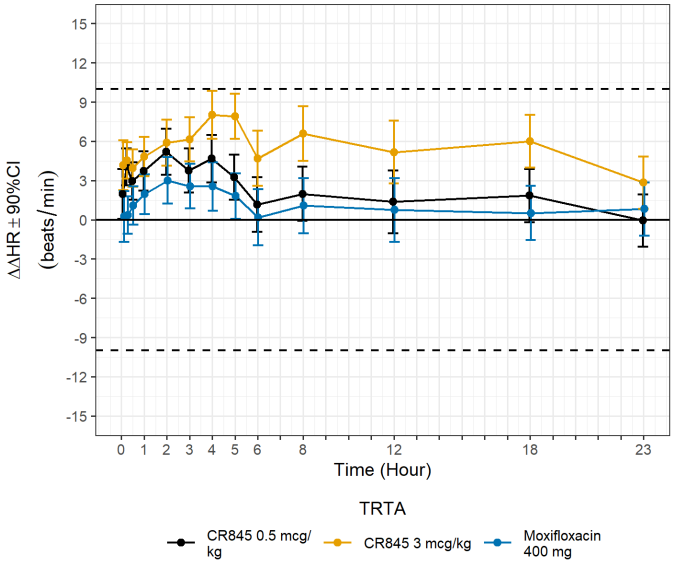
Table 3: The Point Estimates, the 90% CIs, and the 97.5% CIs Corresponding to the Largest Lower Bounds for ΔΔQTcF

Actual Treatment	N	Time (hours)	ΔΔQTcF (msec)	90.0% CI (msec)	97.5% CI (msec)
Moxifloxacin 400 mg	50 / 51	4.0	12.5	(10.3 to 14.7)	(9.4 to 15.5)

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

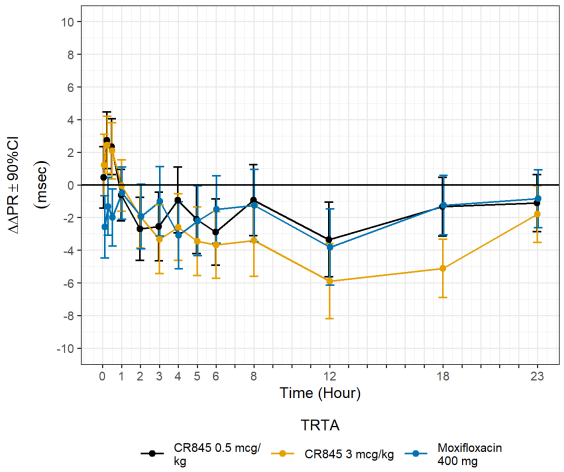
Figure 2: Mean and 90% CI of ΔΔHR Timecourse



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

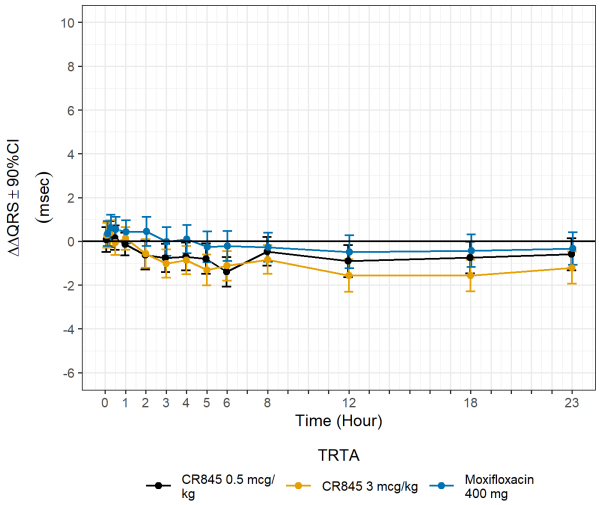
Figure 3: Mean and 90% CI of ΔΔPR Timecourse



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4: Mean and 90% CI of ΔΔQRS Timecourse



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs.

4.4.1 QTc

None of the subjects experienced QTcF greater than 480 msec and/or none of the subjects experienced ΔQTcF greater than 60 msec in any of the CR845 dose groups.

4.4.2 HR

Table 4 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min). There was one subject who experienced HR greater than 100 beats/min in CR845 0.5 mcg/kg dose group.

Table 4: Categorical Analysis for HR (maximum)

Actual Treatment	Total (N)		Value <= 100 beats/min		Value > 100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
CR845 0.5 mcg/kg	54	700	53 (98.1%)	698 (99.7%)	1 (1.9%)	2 (0.3%)
CR845 3 mcg/kg	53	685	53 (100.0%)	685 (100.0%)	0 (0%)	0 (0%)
Placebo	52	672	52 (100.0%)	672 (100.0%)	0 (0%)	0 (0%)

4.4.3 PR

None of the subjects experienced PR above 220 msec with and without 25% increase over baseline in any of the CR845 dose groups.

4.4.4 QRS

None of the subjects experienced QRS above 120 msec with and without 25% increase over baseline in any of the CR845 dose groups.

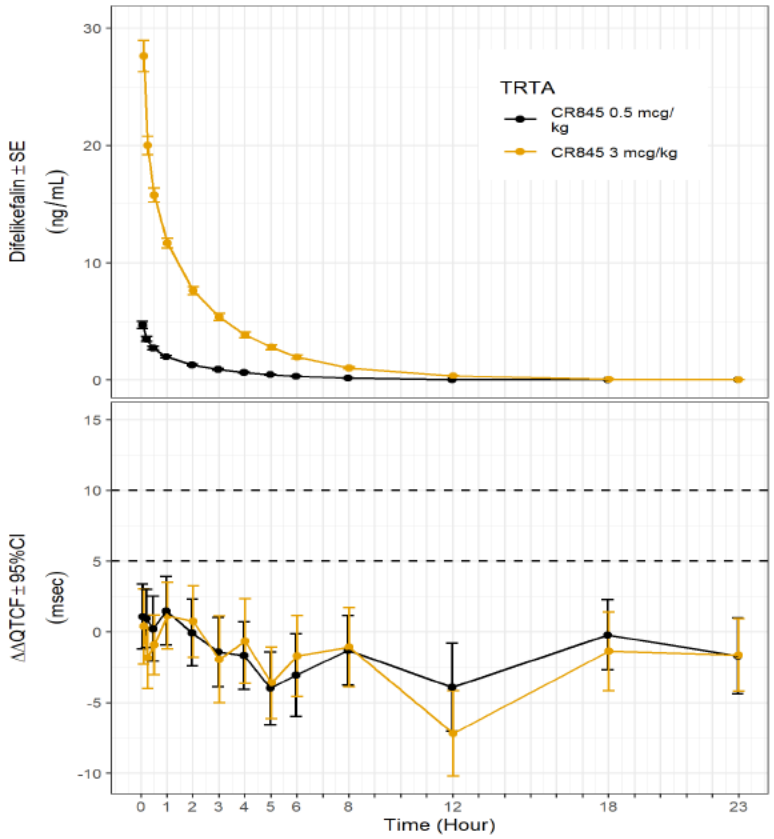
4.5 Exposure-Response Analysis

The objective of the clinical pharmacology analysis was to assess the relationship between plasma concentration of difelikefalin and ΔQTcF. Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK.

Prior to evaluating the relationship between difelikefalin concentration and QTc using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between difelikefalin concentration and ΔQTc and 3) presence of non-linear relationship.

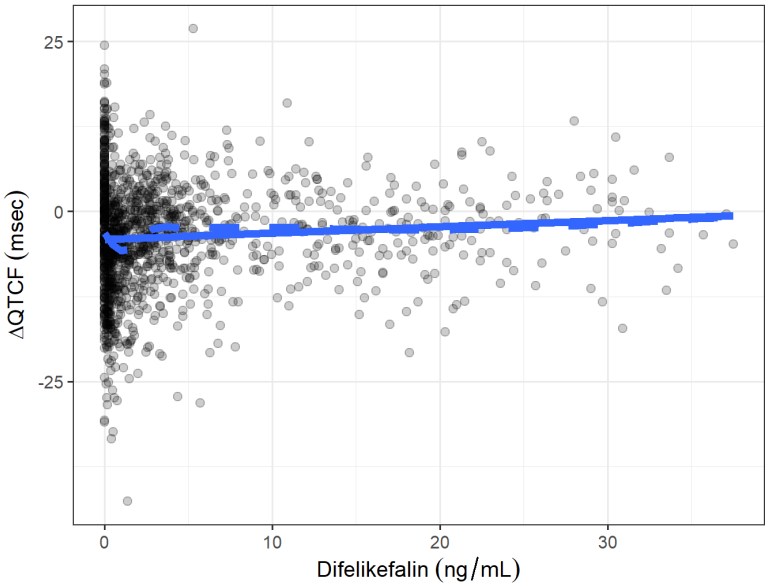
An evaluation of the time-course of difelikefalin concentration and changes in ΔΔQTcF is shown in Figure 5. There was no apparent correlation between the time at maximum effect on ΔΔQTcF and peak concentrations of difelikefalin indicating no significant hysteresis. Figure 2 shows the time-course of ΔΔHR, which shows an absence of significant ΔΔHR changes and the maximum change in heart rate is below 10 bpm (Sections 4.3.2 and 4.4.2).

Figure 5: Time course of difelikefalin concentration (top) and QTc (bottom)



After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between difelikefalin concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between difelikefalin concentration and ΔQTcF and supports the use of a linear model.

Figure 6: Assessment of linearity of concentration-QTc relationship



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTc model are provide in Table 5.

Figure 7: Goodness-of-fit plot for QTc

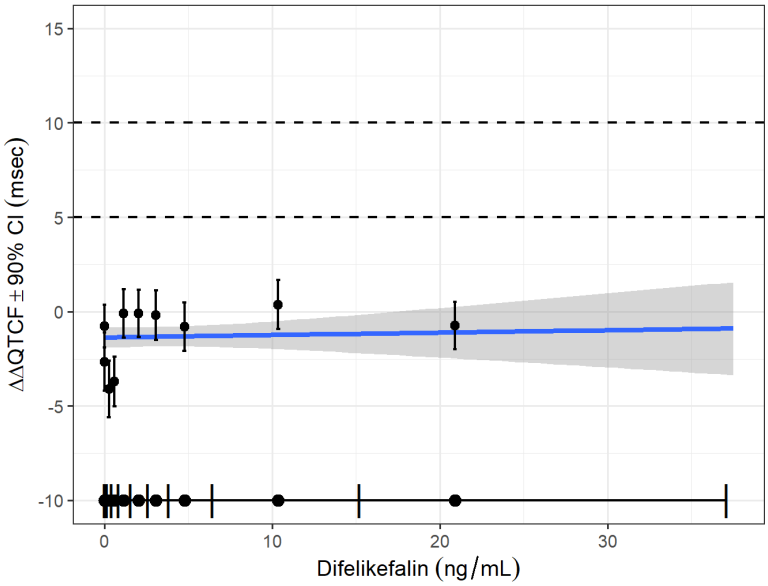


Table 5: Predictions from concentration-QTc model

Actual Treatment	Analysis Nominal Period Day (C)	Difelikefalin (ng/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
CR845 0.5 mcg/kg	1	4.6	-1.3	(-1.8 to -0.8)
CR845 3 mcg/kg	1	27.2	-1.0	(-2.8 to 0.7)

4.5.1 Assay sensitivity

To demonstrate assay sensitivity, the sponsor included oral moxifloxacin 400 mg as a positive control detecting small increases from baseline for QTcF in this study.

The PK profile in the moxifloxacin group are generally consistent with the ascending, peak, and descending phases of historical data (data not shown). Concentration-response analysis of moxifloxacin data indicated a positive slope in the relationship between ΔΔQTcF and the plasma concentration of moxifloxacin. The predicted lower limit of the two-sided 90% confidence interval at the observed mean peak concentrations (Cmax) following 400 mg moxifloxacin single dose is above 5 ms (Table 6). Therefore, assay sensitivity is established. The goodness-of-fit plot for moxifloxacin is shown in Figure 8.

Figure 8: Goodness-of-fit plot for ΔΔQTcF for moxifloxacin

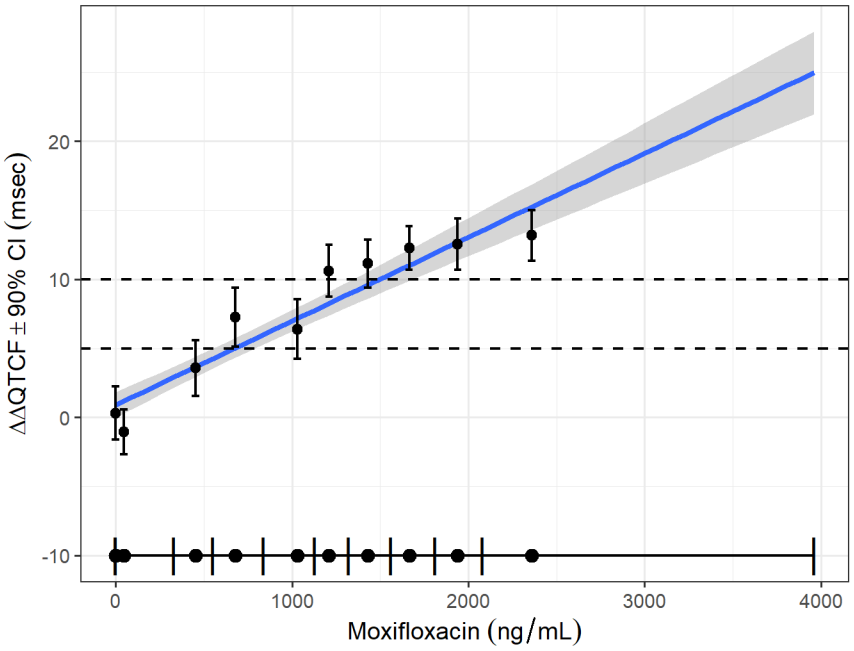


Table 6: Predictions from concentration-QTc model for moxifloxacin

Actual Treatment	Moxifloxacin (ng/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
Moxifloxacin 400mg	2,001.7	13.1	(11.7 to 14.4)

Assay sensitivity was also established using by-time analysis. Please see Section 4.3.1.1 for additional details.

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/s/

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